in this study. Peak exposures were therefore estimated by an industrial hygienist from knowledge of the job tasks and a comparison with the 8-hour time-weighted average" (Hauptmann et al., 2003, p. 1616; Stewart et al., 1986). Stewart et al. (1986) reported that the exposure reconstruction included rating confidence (i.e., confident, less confident, not confident) in the exposure estimate; however, the "confidence" category appeared to apply to the "rank" exposure and not the "peak exposure." For example, if an IH specified "not confident" for an average exposure estimate, it is not clear how or if this information applied to the estimate of peak exposure (categorized during data collection as 1 = none, 2 = 0.1–0.5, 3 = 0.51–2.0, 4 = 2.1–4.0, 5 = > 4.0, 9 = unknown) (Stewart et al., 1986).

In extended analyses of the NCI cohort study, Checkoway et al. (2015) refined the classification of peak exposure. Workers who did not work in jobs identified as likely having peak exposures were classified as not exposed to peaks, and became the referent group. A total of 3478 cohort members were classified as having worked in jobs with estimated peak exposure of 2- < 4 ppm, and 2907 worked in jobs with estimated peak exposure of ≥ 4 ppm. Analysis by ML subtype (i.e., AML and CML deaths, separately) found no association between peak exposure and AML mortality (HR 1.71, 95% CI 0.72–4.07 and HR 1.43, 95% CI 0.56–3.63, respectively) (Checkoway et al., 2015). However, 13 of the 34 AML deaths were classified as having worked in jobs likely having peak exposure > 2.0 ppm, only 4 of which worked in these jobs within the 20 years preceding their AML death (i.e., latest exposure), and only one occurred (similar to the number expected) within the typical AML latency window of 2–15 years. Upon fuller analyses of these data, Checkoway et al. (2015) subsequently found that only a third of all the AML deaths were among cohort members assigned to categories with any peak exposure (i.e., > 2.0 ppm), nearly all of whom had their last peak exposure more than 20 years earlier, well outside of the maximum latency window.

Coggon et al. (2014) also reported that limited IH data were available for the UK formaldehyde users and producers cohort, preventing the derivation of quantitative metrics. Nevertheless, the investigators expressed high confidence that the high exposure category corresponded to average concentrations of at least 2 ppm. Industrial hygiene data also were limited in the US NCI industrial workers study, although the investigators used them as part of a detailed exposure reconstruction using best practices for such a reconstruction at the time. Stewart et al. (1986) reported that historical exposure levels were estimated because most companies did not begin sampling until the mid-1970's: they also monitored "present day" (i.e., early 1980's) operations to help extrapolate historical exposures. The NCI investigators relied upon exposure rank (six levels of TWA): trace, < 0.1 ppm, 0.1–0.5 ppm, 0.51–2.0 ppm and > 2 ppm.

One criticism leveled at the UK worker cohort study (Acheson et al., 1984; Coggon et al., 2003, 2014; Gardner et al., 1993) was that the "authors reported a concern about the quality of data when they made exposure assignments" (NRC, 2014b). This criticism seems to stem from the appropriate identification and discussion of study limitations by earlier UK investigators: Gardner et al. (1993) reported "when jobs were being placed into qualitative categories of exposure in the British study, some disagreement occurred as to which of two adjacent grades was most appropriate-for example, high or moderate? To achieve consistency across all the factories, the higher of the two was always used. It is not clear how differences were resolved in the United States study." Thus, there are no essential differences in the approach used by the UK investigators and the US investigators: both studies reported that limited data were available on quantitative exposure measures using existing industrial hygiene data (from the 1980s); both exposure assessments allowed for the consideration of changes in processes and exposure controls during the period of the study; and both used ranked categories of exposure, developed before the estimation process, based somewhat on subjective sensory experiences encountered in the job (e.g., odor occasionally present), and both used eye irritation and odor throughout the day to identify the highest intensity of exposure jobs (Acheson et al., 1984; Stewart et al., 1986).

Ultimately, the Beane Freeman et al. (2009) study alone does not (and cannot) provide reliable support for a conclusion that peak formaldehyde exposure causes ML or AML, especially considering the absence of peak measurement data in the US study, the results of the reanalysis by Checkoway et al. (2015), and the updated results from the UK study (Coggon et al., 2014), which used a more conservative approach to exposure estimation.

3.1.3. Synthesis of epidemiology studies: evaluation of the most specific diagnosis

The NRC (2011) raised the issue that diverse types of leukemias and lymphomas should not be grouped "because it combines many diverse cancers that are not closely related in etiology and cells of origin. Although the draft IRIS assessment explores specific diagnoses—such as AML and CML, as well as Hodgkin lymphoma and multiple myeloma (see, for example, EPA 2010, Tables 4–92)—the determinations of causality are made for the heterogeneous groupings of "all LHP cancers," "all leukemias," and "ML". When results for heterogeneous groupings are presented, there is no evidence of increased risk of all LHP cancers (Meyers et al., 2013; Beane Freeman et al., 2009) or all leukemias combined (Coggon et al., 2014; Meyers et al., 2013; Beane Freeman et al., 2009) in industrial cohorts when compared to general mortality rates. In addition, there is no evidence of exposure-response associations between all LHPs combined (or all leukemias combined) and cumulative exposure or average exposure (Beane Freeman et al., 2009) or duration of exposure (Meyers et al., 2013; Coggon et al., 2014).

Interestingly, the Draft IRIS Assessment noted that "Acute leukemias (ALL and AML), believed to arise from transformation of stem cells in the bone marrow, are less plausible. In contrast chronic lymphatic leukemia, lymphomas, multiple myelomas (from plasma B cells), and unspecified cancers may involve an etiology in peripheral tissues to include cells, cell aggregates, germinal centers, and lymph nodes. An association of these cancers to an exogenous agent acting at the POE [portal of entry] is biologically plausible" (EPA, 2010; page 4–190).

While the etiologies of most LHM are poorly understood, the possible role of environmental agents is plausible for AML, which has been linked with benzene, tobacco smoking, ionizing radiation and various cancer treatment agents, such as cisplastin, all of which have been classified by IARC as known human carcinogens that cause AML. It should be stressed that evidence exists that these agents, or their carcinogenic components, are capable of reaching the bone marrow. However, only six epidemiological studies of workers substantially exposed to formaldehyde published to date have published AML-specific results (Blair et al., 2001; Checkoway et al., 2015; Hauptmann et al., 2009; Meyers et al., 2013; Saberi Hosnijeh et al. 2013; Talibov et al., 2014), four of which were not available at the time of the IARC review or the release of the Draft IRIS Assessment. Saberi Hosnijeh et al. (2013) reported no association between "low" formaldehyde exposure and incidence of myeloid leukemia (HR 1.02, 95% CI 0.72–1.42 based on 49 cases exposed to formaldehyde and 130 unexposed cases). No differences were seen between subtypes: AML (HR 1.01, 95% CI 0.65–1.57) or CML (HR 0.92, 95% CI 0.46–1.84). No myeloid cases (and therefore no AML cases or CML cases) occurred among those classified as having "high" formaldehyde exposure (Saberi Hosnijeh et al., 2013). Talibov et al. (2014) found no association between formaldehyde and incident AML, after adjusting for exposure to specific solvents and ionizing radiation (HR 1.17, 95% CI 0.91–1.51 for 136 workers and 628 controls exposed to > 1.6 ppm-yrs). Meyers et al. (2013) reported a SMR for AML of 1.22 (95% CI 0.67–2.05) based on 14 observed AML deaths. Checkoway et al. (2015) performed AML-specific analysis using the NCI cohort, which had provided results only for all ML combined (Beane Freeman et al., 2009). When compared to US referent rates, AML mortality risk was decreased among workers

exposed to formaldehyde (SMR 0.80, 95 %CI 0.46–1.14) and internal analysis of exposure reported no trend with increasing cumulative exposure or peak exposure categories (Checkoway et al., 2015). Thus, new analyses of the NCI formaldehyde workers cohort specifically for AML detract from the hypothesis that formaldehyde causes AML.

The associations reported by Beane Freeman et al. (2009) between formaldehyde exposure and Hodgkin lymphoma and CML have not been observed in other studies (Meyers et al., 2013; Saberi Hosnijeh et al., 2013) and are less plausible, given the lack of known associations with Hodgkin lymphoma or CML and other chemicals or agents, such as benzene (Checkoway et al., 2015). Saberi Hosnijeh et al. (2013) reported a RR of 0.92 (95% 0.46 to 1.84) based on 46 CML cases. Meyers et al. (2013) reported a SMR of 1.35 (95% CI 0.44–3.15), based on 5 CML cases through 2008. The absence of established toxicological mechanisms for formaldehyde exposure and any of the LHM further weakens arguments for causation (Checkoway et al., 2012, 2015), especially given that inhaled formaldehyde appears incapable of reaching the bone marrow (discussed in Section 3.3).

3.2. Toxicological evidence

3.2.1. Animal evidence of formaldehyde-induced LHM

With regard to animal evidence of formaldehyde-induced LHM, the Draft IRIS Assessment (EPA, 2010) stated that the available animal evidence is limited, discussing mainly the results from the Battelle Columbus Laboratories (1981) study. The Draft IRIS assessment indicated that this study provides the only evidence of formaldehyde-induced LHM in animal models. However, the NRC (2011) peer review noted that although intriguing, EPA's unpublished re-analysis of the Battelle chronic experiments in mice and rats (Battelle Columbus Laboratories, 1981) contributed little to the weight of evidence evaluation.

In rats, Battelle Columbus Laboratories (1981) reported the incidence of leukemia (most of which were diagnosed as undifferentiated leukemia found sporadically in various organs) in male and female Fischer 344 rats following exposure to concentrations of 0, 2, 6, or 15 ppm for 24 months, followed by 6 months with no exposure. No concentration-related increases in the incidences of leukemia in either sex of rats were reported by Battelle Columbus Laboratories (1981), when a standard Fisher-Irwin exact test was applied (males $p = 0.0972$; females $p = 0.2316$).

Because of a significant number of early deaths in the high concentration group of both males and females, Battelle Columbus Laboratories (1981) also applied Tarone's extension to the Cox log-rank test (Tarone, 1975) to evaluate the leukemia incidence data. This test accounts for the number of animals at risk at each time point when the response of interest is observed. This adjustment assessed the probability of developing the endpoint of interest in those animals that did not survive until the termination of the study. The results of Tarone's extension indicated that the incidence among female rats in the high concentration group was statistically significant ($p = 0.0056$, not 0.0003 as reported[3]); however, no association was seen in the male rats exposed at high concentrations ($p = 0.6891$). No concentration-related increase in leukemia was observed in the female rats exposed at either 2 ppm or 6 ppm, and no survival problems were noted. Even after application of Tarone's extension, leukemia in male or female rats was not identified in the Battelle Columbus Laboratories (1981) study as an endpoint related to formaldehyde exposure, nor was it so designated in two publications citing this study (Kerns et al., 1983; Swenberg et al., 2013).

More contemporary statistical methods, such as the Cochran-Armitage and the Poly3 (Bailer and Portier, 1988; Peddada and Kissling, 2006) trend tests, have replaced those used in the early 1980's. The Poly3 trend test is a survival-adjusted quantal-response procedure that modifies the Cochran-Armitage linear trend test to take inter-group survival differences into account. Importantly, the Poly3 test is the test currently used by the National Toxicology Program (NTP) to evaluate incidence data both for trend and pair-wise comparisons, to assess the probability of the response in the presence of inter-current mortality. The results of the application of these tests indicated p values of 0.43 and 0.82 for the Poly3 and Cochran-Armitage, respectively, demonstrating no association.

In mice, the Draft IRIS Assessment (EPA, 2010) suggested that the "adjusted" incidence of lymphoma in female mice, when the 6-month sacrifice animals were removed from consideration (because tissues outside of the respiratory tract were not examined), was statistically significant ($p < 0.05$) in animals exposed to 15 ppm formaldehyde, compared to untreated controls. However, as indicated in the methods for the Battelle Columbus Laboratories (1981) study, statistical significance, when applying the Tarone extension of the Cox test, is achieved with a p value of 0.05 divided by the number of dose groups. In the case of the Battelle Columbus Laboratories (1981) study for the mouse data, statistical significance would be $p < 0.0167$, as noted in the summary tables (Table 8 of the Battelle Columbus Laboratories (1981) report); therefore, based on this criterion, this endpoint was not considered statistically significant. As with the leukemia incidence in rats, the Battelle study authors did not report lymphoma in mice as an endpoint related to formaldehyde exposure.

Since 2010, two short-term carcinogenicity studies have been conducted and published (as a Technical Report) by the NTP of NIEHS in strains of genetically predisposed mice (male C3B6·129F1-Trp53tm1Brdp53 haplo-insufficient mice and male B6.129-Trp53tm1Brd) (Morgan et al., 2017). These short-term carcinogenicity studies were conducted to test the hypothesis that formaldehyde inhalation would result in an increased incidence and/or shortened latency to nasal and lymphohematopoietic tumors and to investigate hypotheses that formaldehyde may induce leukemia by a mechanism not involving DNA adduct formation. This proposed mechanism assumes that inhaled FA could cause significant genetic damage to stem cells in the nasal epithelium or circulating in local blood vessels. These damaged stem cells could reach the general circulation, home to tissues that support the hematopoietic niche, undergo lodgement and become leukemic stem cells. The animals were exposed to 7.5 or 15 ppm formaldehyde 6 hours/day, 5 days/week, for 8 weeks. The investigators reported that because the doubling time for hematopoietic stem and progenitor cells (HSPCs) is between 2 and 4 weeks, and the entire HSPC pool turns over every 8 weeks, an 8 week exposure duration was considered sufficient to investigate the hypothesized mechanism for inducing leukemia. Following the 8-week inhalation exposure, mice were monitored for approximately 32 weeks (until approximately 50 weeks of age). At the highest concentrations, significant cell proliferation and squamous metaplasia of the nasal epithelium were observed; however, no nasal tumors were observed. No cases of leukemia were seen in either strain and a low incidence of lymphoma in exposed mice was not considered related to exposure. In addition, no significant changes in haematological parameters were noted. Under the conditions of these studies, the authors concluded that formaldehyde inhalation did not cause leukemia in these strains of genetically predisposed mice (Morgan et al., 2017).

Overall, the weight of evidence from animal studies reported in the Draft IRIS Assessment (EPA, 2010) did not support an association between formaldehyde exposure and LHM. Since that time, additional studies (Morgan et al., 2017) have provided evidence that suggests a lack of association between formaldehyde exposure and LHM. In addition, no evidence of changes in blood parameters that might be

[3] This appears to be a misreading of the Battelle report. In the Battelle Report Volume A Table 10 – Analysis of Effects of Formaldehyde in Female Rats - reports a p-value of 0.0056 from the Adjusted Cox/Tarone pair-wise comparison of the control to 15 ppm for Leukemia, all. The next row in that table with an endpoint of Uterus, Endometrial Stromal Polyp is the one that reports a p-value of 0.0003 for the pair-wise analysis of control to 15 ppm.

associated with leukemias has been reported in any animal studies exposed to formaldehyde at high concentrations following both acute and chronic durations (Appelman et al., 1988; Dean et al., 1984; Johannsen et al., 1986; Kamata et al., 1997; Kerns et al., 1983; Til et al., 1988, 1989; Tobe et al., 1989; Vargova et al. 1993; Woutersen et al., 1987). Among these studies, Vargová et al. (1993) reported *increased* red blood cell counts and *increased* proportions of lymphocytes and monocytes in rats, rather than decreases, following exposure to formaldehyde by gavage at 80 mg/kg/day for 28 days.

3.3. Mode of Action Evidence

3.3.1. Improve understanding of when exogenous formaldehyde exposure appreciably alters normal endogenous formaldehyde concentrations

NRC (2011) recommended that one key improvement to the science would be an understanding of when exogenous formaldehyde exposure altered normal endogenous formaldehyde concentrations. Because formaldehyde is endogenously present, it is important to differentiate levels that are due to normal metabolic processes from levels that might be present as a result of exogenous exposure. A number of studies have applied sensitive methods to differentiate exogenous and endogenous levels of formaldehyde in tissues (Casanova-Schmitz et al., 1984; Lu et al., 2010, 2011; Moeller et al., 2011; Swenberg et al., 2011).

The results of these studies with highly sensitive instruments and accurate assays indicate that inhaled formaldehyde was present in the nasal respiratory epithelium, but not other tissues beyond the site of initial contact. In contrast, endogenous adducts were readily detected in all tissues examined. Moreover, the amounts of exogenous formaldehyde-induced adducts were 3- to 8-fold and 5- to 11-fold lower than the average amounts of endogenous formaldehyde-induced adducts in rat and monkey nasal respiratory epithelium, respectively (Yu et al., 2015).

An additional study conducted in rats exposed to ^{13}C-formaldehyde (Kleinnijenhuis et al., 2013) provided results consistent with those from studies focused on measuring endogenous versus exogenous DNA adducts. In this study, Sprague-Dawley rats were exposed nose-only to 10 ppm ^{13}C-formaldehyde for 6 hours and blood concentrations evaluated during exposure and for 30 minutes following exposure. This study was conducted specifically to investigate the mechanism proposed by Zhang et al. (2010a) that formaldehyde is absorbed during respiration and could reach any target tissue, such as the bone marrow, via the blood in the form of methanediol to exert its genotoxic activity. Exogenous ^{13}C-formaldehyde was not detectable in the blood of rats either during or up to 30 min after the exposure. The authors concluded that "it is highly unlikely that the mechanism proposed by Zhang et al. (2009), that exposure to FA by inhalation may lead to an increased FA concentration in blood and as such may cause leukemia, is true" (Kleinnijenhuis et al., 2013).

New studies have been conducted to investigate the potential toxicity/carcinogenicity of endogenous formaldehyde. The most recent studies demonstrate that endogenous formaldehyde in bone marrow is toxic, and probably carcinogenic, and therefore may increase leukemia risk (Pontel et al., 2015; Lai et al., 2016).

3.3.2. Reconcile divergent statements regarding systemic delivery

Multiple studies in rats (Lu et al., 2011; Yu et al., 2015; Edrissi et al., 2013) and monkeys (Moeller et al., 2011; Yu et al., 2015) conducted with sensitive analytical methods that can measure endogenous versus exogenous formaldehyde DNA or protein adducts have demonstrated that inhaled exogenous formaldehyde is not systemically absorbed or reaches sites distant from the point of initial contact. In addition to these studies, the available data on the toxicokinetics of formaldehyde suggest that no significant amount of "free" formaldehyde would be transported beyond the portal of entry.

In addition to studies supporting the lack of systemic delivery of formaldehyde, anatomically accurate computational fluid dynamics (CFD) models of the rat, monkey, and human have been applied to evaluate the effects of endogenously present formaldehyde on uptake from the respiratory tract. The consideration of endogenous formaldehyde concentrations in nasal tissues did not affect flux or nasal uptake predictions at exposure concentrations > 500 parts per billion (ppb); however, reduced nasal uptake was predicted at lower exposure concentrations (Schroeter et al., 2014).

3.3.3. Data are insufficient to conclude formaldehyde is causing cytogenetic effects at distant sites

The modes of action that have been proposed in the Draft IRIS Assessment (EPA, 2010) to cause leukemogenesis rely strongly on the hypothesis that exposure to inhaled formaldehyde can result in cytogenetic effects at sites distant from the portal of entry. While the NRC (2011) noted that numerous studies have shown genotoxic effects in cells exposed *in vitro*, and a few studies have shown positive cytogenetic effects in circulating blood lymphocytes in heavily-exposed workers, they also noted that it is unlikely that these effects are relevant to a possible leukemogenic effect of formaldehyde, particularly at low exposure levels. The potential leukemogenic effect and exposure-response relationships at lower exposure levels have been comprehensively evaluated by Nielsen et al. (2013, 2017).

One key study cited in multiple agency evaluations as providing evidence of cytogenetic events in the development of leukemias is by Zhang et al. (2010a, 2010b) compared the prevalence of markers of hematopoietic function and chromosomal aneuploidy among workers occupationally exposed to formaldehyde with those of a group of unexposed workers in China. Ninety-four workers were included, with 43 workers occupationally exposed to formaldehyde and 51 workers unexposed to formaldehyde as controls. The authors reported a higher prevalence of monosomy 7 (loss of a chromosome) and trisomy 8 (gain of a chromosome) in metaphase spreads prepared from cultures of CFU-GM colony cells. The authors suggested that this demonstrated that formaldehyde exposure was associated with an increase in leukemia-specific chromosomal aneuploidy *in vivo* in the hematopoietic progenitor cells of the exposed workers. However, no direct *in vivo* metaphases had been examined in workers blood. Furthermore, this was a cross-sectional comparison of blood and cytogenetic measures between two groups, and observed differences could not be established as resulting from formaldehyde exposure or due to other overall differences between the two groups.

Two re-analyses of the underlying data from the Zhang et al. (2010a) study have been published (Gentry et al., 2013; Mundt et al., 2017). The first (Gentry et al., 2013) relied upon selected underlying data provided through a Freedom of Information Act request that included: 1) individual data on blood cell counts in both formaldehyde-exposed and unexposed individuals including any data on health status of these individuals; 2) individual data on the FISH results for monosomy 7 and trisomy 8 for cultures of samples obtained from 10 formaldehyde-exposed workers and 12 unexposed controls; 3) data on additional chromosomal abnormalities examined and/or observed; and 4) details of the methods sufficient for a qualified scientist to replicate the results reported in the Zhang et al. (2010) study. The results of this reanalysis suggested that factors other than formaldehyde exposure likely contributed to the reported findings. In addition, although the authors stated in their paper that "all scorable metaphase spreads on each slide were analyzed, and a minimum of 150 cells per subject was scored," this protocol was not followed specifically for chromosome 7 or chromosome 8 (recent correspondence indicates a minimum of 150 total metaphases were scored for 24 chromosomes per subject). Far too few cells were counted to draw any meaningful conclusions, and far fewer than the approximately 400 per chromosome cited in previous analyses in which the protocol was described (Zhang et al., 2005, 2011). In addition, the assays used (CFU-GM) do not actually measure the proposed events in primitive cells involved in the development of AML. Evaluation of these data indicates that the aneuploidy measured

could not have arisen *in vivo*, but rather arose during *in vitro* culture.

In 2014, Mundt et al. requested the individual exposure measurement data for each of the participants in the Zhang et al. (2010a) study from NCI. In 2016, the request was in part granted and the mean formaldehyde estimate for each exposed worker (but not the individual exposure measurement values) was provided via a Technology Transfer Agreement (TTA) with NCI. Using these data, the Gentry et al. (2013) reanalysis was extended to include exposure-response analyses. Results of this second reanalysis showed that differences seen at the group comparison level, i.e., comparing the prevalence of white blood cell, granulocyte, platelet, and red blood cell counts at the group level in fact were independent of measured formaldehyde exposure level. Among exposed workers, no association was observed between individual average formaldehyde exposure estimates and frequency of aneuploidy, suggested by the original study authors to be indicators of ML risk. Differences between the two groups of workers, other than formaldehyde exposure, were therefore likely to explain the results reported by Zhang et al. (2010a).

Subsequent studies of the same population of formaldehyde-exposed and non-exposed workers in China (Lan et al., 2015; Seow et al., 2015; Bassig et al., 2016) have been suggested by the authors to confirm the results of Zhang et al. (2010a); however, many of these studies report results from the same biological samples as Zhang et al. (2010a) and therefore, do not provide replication of the results. The repeated use of the original Zhang et al. (2010a) data, and its implications, have been reiterated (Pira et al., 2017; Gentry et al., 2013; Speit et al., 2010) and the original authors have responded to some of the criticisms (Rothman et al., 2017; Lan et al., 2015; Zhang et al., 2010b). Replication of the Zhang et al. (2010a) results will require replication in an independent population of formaldehyde-exposed workers, and where methodological issues are adequately addressed. An attempt to replicate the results could be conducted in the same population of workers as Zhang et al. (2010a) and Lan et al. (2015) in which the median exposures to 43 workers were 1.28 ppm (10th and 90th percentile: 0.63, 2.51 ppm). However, as noted previously (Section 3.1.1), no evidence of an association between formaldehyde exposure and leukemias has been reported in multiple recent epidemiological studies with large numbers of subjects that have been exposed to concentrations > 2.0 ppm. The increasing evidence that inhaled formaldehyde does not move beyond the portal of entry (Section 3.3.2) also calls into question many of the conclusions from Zhang et al. (2010a).

Albertini and Kaden (2016) reviewed the body of data that reportedly indicates genetic changes in circulating blood cells and in blood-borne hematopoietic precursor cells (HPCs). These changes have been considered to be indicators that systemic genotoxicity occurs after human inhalation exposure to formaldehyde, although the mechanisms by which this could occur remain unknown. For each study, the authors examined the sources of exposure, possible co-exposures, biomarkers for internal exposures and genetic signatures of formaldehyde effects.

In reviewing the available studies, many genetic changes in blood cells were noted by Albertini and Kaden (2016), with a contrast in results between animal and human studies: the majority of animal studies were negative and the majority of human studies were positive. This pattern was attributed to the difference in target cell being studied, with bone marrow cells studied in animals and peripheral blood lymphocytes studied in humans. Exposure of human cells to formaldehyde at sites of contact *in vivo* could provide opportunities for exposure of T-lymphocytes to formaldehyde or products of oxidative stress, which could result in the genetic changes observed in peripheral blood cells. However, these results are inconsistent with results from controlled animal studies, discussed previously, that demonstrate - by labeling administered formaldehyde - inhaled (exogenous) formaldehyde does not travel beyond the portal of entry (Casanova-Schmitz et al., 1984; Lu et al., 2010, 2011; Moeller et al., 2011; Swenberg et al., 2011). Therefore, these types of genetic changes reported in human studies do not provide evidence that formaldehyde moves beyond the portal of entry to the bone marrow, which would be necessary to result in direct induction of chromosome-level mutations in the bone marrow. Despite the apparent inability of exogenous formaldehyde to reach the bone marrow, the mutagenic effects of formaldehyde in bone marrow have not been tested in humans.

Albertini and Kaden (2016) concluded that overall, the available literature on genetic changes following formaldehyde exposure did not provide convincing evidence that exogenous exposure, and specifically exposure by inhalation, induces mutations as a direct DNA-reactive effect at sites distant from the portal-of-entry tissue. This would include proposed mode of actions that involve a stem cell effect at the portal of entry with circulation back to the bone marrow. Such exposures have not been shown to induce mutations in the bone marrow or in any other tissues beyond the point of contact. Thus, the weight of scientific evidence does not provide biological plausibility of lymphohematopoietic cancers, as proposed by EPA (2010) and NTP (2011).

3.4. Dose-response assessment

Several NRC (2011) peer-review comments were raised regarding the dose-response assessment conducted by EPA in the Draft IRIS Assessment (2010). One comment highlighted the need to conduct independent analyses of the dose-response models, using the data from the Beane Freeman et al. (2009) study to confirm which models fit the data appropriately (NRC, 2011). Using the original data from the key study (Beane Freeman et al., 2009) and documentation provided in the Draft IRIS Assessment, Van Landingham et al. (2016) attempted to duplicate the reported inhalation unit risk (IUR) values for Hodgkin lymphoma and all leukemias and address the NRC Committee's questions regarding application of the appropriate dose-response model. Overall, there was difficulty duplicating the IURs reported by EPA (2010), largely due to a lack of critical information provided in the IRIS documentation. Perhaps most problematic, the first step of the analysis did not determine significant exposure-response relationships between formaldehyde and lymphohematopoietic endpoints for the metric (cumulative exposure) needed in the estimation of an IUR. The authors concluded that the resulting analysis, while it could be mechanically performed, provided no valid or useful insights on the risks of formaldehyde exposure. The lack of apparent exposure-response relationships for selected endpoints raises the question whether quantitative analyses are appropriate for these endpoints, and if so, how results are to be interpreted.

The NRC (2011) also noted the need to consider alternative extrapolation models for analyzing the cancer data. In 2013, Starr and Swenberg proposed a novel "bottom-up" approach for bounding low-dose human cancer risks using formaldehyde as an example (Starr and Swenberg, 2013). This approach requires information on background risk, background or endogenous exposure and the additional exogenous exposure of interest. The results of this approach provided estimates of risk ($< 3.9 \times 10^{-6}$) that were more than 14,000-fold lower than the corresponding Draft IRIS Assessment (EPA, 2010) estimate for all leukemias (5.7×10^{-2}) and considers the impact of background endogenous formaldehyde concentrations, which is not considered in the Draft IRIS Assessment (EPA, 2010). In 2016, Starr and Swenberg provided an update to this approach, incorporating new formaldehyde-DNA adduct data, and allowing for uncertainty in two of the parameters (background cancer risk and background endogenous concentrations of formaldehyde) (Starr and Swenberg, 2016). Consideration of the statistical uncertainty in these two parameters resulted in estimates of risk for leukemias that were even smaller than those initially estimated in Starr and Swenberg (2013). The authors concluded that these estimates provide a reality check for the IUR presented in the Draft IRIS Assessment (EPA, 2010). In addition, the large discrepancy between results using an approach that relies on molecular dosimetry data (i.e., the bottom up approach) versus one that relies upon uncertain retrospective occupational exposure reconstructions (i.e., the approach

relied upon in EPA (2010) call into question the credibility of attributing increases in human mortality from leukemias to occupational exposure to formaldehyde.

3.5. Methods for evidence integration

The NRC (2011) noted that the Draft IRIS Assessment's (EPA, 2010) approach to weight of evidence should include "a single integrative step after assessing all of the individual lines of evidence". Although a synthesis and summary are provided, the process that EPA used to weigh different lines of evidence and how that evidence was integrated into a final conclusion are not apparent in the draft assessment and should be made clear in the final version.

Since the Draft IRIS Assessment (EPA, 2010) and the NRC (2011) peer review, several frameworks have been developed to integrate evidence across different lines of scientific inquiry including epidemiology, toxicology and mode of action studies (Adami et al., 2011; Lavelle et al., 2012; Linkov et al., 2015; Rhomberg, 2015b; Rooney et al., 2014; Woodruff and Sutton, 2014). The EPA has also proposed preliminary approaches for integrating evidence in response to the NRC (2011) peer review of formaldehyde (EPA, 2013a).

Rhomberg et al. (2011) applied a hypothesis-based weight of evidence approach to evaluate formaldehyde and leukemogenesis, considering how human, animal and mode of action results inform one another. In comparing the potential alternative proposals for causality, the authors concluded that the evidence for a causal association between formaldehyde exposure and leukemia is not only weak but strains biological plausibility (Rhomberg et al., 2011).

Nielsen et al. (2017) also considered the body of formaldehyde research while re-evaluating the WHO (2010) formaldehyde indoor air quality guideline for cancer risk assessment. Nielsen et al. (2017) iterated that although formaldehyde is genotoxic and causes DNA adduct formation, it is also clastogenic. Exposure-response relationships from both animal and human data were nonlinear, and relevant genetic polymorphisms had not been identified. Although one epidemiological study had reported an association with nasopharyngeal cancer and others reported inconsistent associations with leukemias, relative risks were not increased below 1 ppm (mean exposures). Because inhaled formaldehyde does not pass beyond the respiratory epithelium, any direct effects are limited to portal-of-entry effects (Nielsen et al., 2017).

Other reviews and syntheses of evidence focused on epidemiological studies, and this body of literature has been most variably interpreted. In 2014, an independent National Research Council committee was charged with performing a peer review of the NTP evaluation of formaldehyde for the 12th edition of the RoC (NRC, 2014b). This NRC committee produced a new definition for "sufficient evidence" of carcinogenicity as demonstrated by two or more strong or moderately strong epidemiological studies with different study designs and populations showing associations between formaldehyde exposure and a specific cancer type. In this approach, "strong" epidemiology studies do not refer to the magnitude of the association, but relect a judgment of study quality and utility made by reviewers who considered chance, bias, and confounding as alternative explanations for the observed association and found these were not reasonable explanations. Further, "strong" epidemiology studies comprised large populations with long durations of exposure and an adequate follow up period to allow for latency, and had exposure assessments that were able to discriminate between "high" and "low" formaldehyde exposure categories. This "strength of evidence" approach contrasts with a "weight of evidence approach." Although each epidemiology study was classified as one of three categories (strong, moderately strong, or weak), this approach suggests that 2 or more strong or moderately strong studies with positive results are enough to conclude sufficient evidence of carcinogenicity exists, and discounts epidemiology and animal studies that are negative or contradictory.

Meta-analyses are often used to synthesize findings across many epidemiology studies, identifying sources of potential heterogeneity which then can be explored in interpreting the overall evidence. In the Draft IRIS Assessment (EPA, 2010), meta-analyses conducted by several investigators were considered (Zhang et al., 2009; Collins and Lineker, 2004; Bosetti et al., 2008). Since then, two additional meta-analyses were conducted (Bachand et al., 2010; Schwilk et al., 2010). Bachand et al. (2010) excluded lower-quality studies and reported a meta-RR of 1.05 (95% CI 0.93–1.20) based on 16 cohort studies and a meta-OR of 0.99 (95% CI 0.71–1.37) based on 2 case-control studies for all leukemia, reported separately due to heterogeneity. Schwilk et al. (2010) published a meta-analysis of the epidemiological findings on myeloid leukemia, but limited to the highest-exposed sub-group reported in four studies (three cohort and one case-control): RR = 2.47; 95% CI, 1.42 to 4.27. Checkoway et al. (2012) conducted a critical review and synthesis of the epidemiological evidence and concluded that results from epidemiological studies were not consistent and did not show strong results or exposure-response associations. None of these reviews, however, included the results from the extended follow up of the NIOSH garment workers study (Meyers et al., 2013), the extended follow up of the UK producers and users (Coggon et al., 2014) or the extended analyses of the NCI cohort (Checkoway et al., 2015). In addition, meta-analyses and/or critical reviews of epidemiological literature require further integration with other lines of evidence.

4. Conclusions

It has been seven years since the release of the *Draft IRIS Toxicological Review of Formaldehyde* (EPA, 2010). In peer-reviewing this draft report, an NRC Committee raised many substantive questions related specifically to the conclusions drawn in the document and the quantitative estimates of potential toxicity (NRC, 2011). This Committee was tasked with reviewing and commenting on information provided in the draft assessment, and did not independently conduct a review of the primary literature, but did determine that many of EPA's conclusions were not supported by the information and studies cited in the draft assessment. The committee also identified general methodologic problems with the Draft IRIS Assessment, and provided specific comments related to the evaluation of specific studies and conclusions based on the available evidence. The comments related to a causal association between formaldehyde exposure and LHM largely involved the interpretation of the available evidence at that time and the framework in which it was evaluated by EPA (2010). The committee found that EPA's preliminary conclusion that formaldehyde causes leukemia, ML or related hematopoietic cancers appeared to be "subjective' in nature, and that no clear scientific framework had been applied by EPA in reaching that conclusion. The absence of such a framework was judged by the committee as troublesome, given that the scientific evidence on the question was weak (NRC, 2011).

Since the NRC (2011) peer review, significant additional scientific evidence has become available that addresses many of the questions raised by the NRC Committee regarding a causal association between formaldehyde exposure and LHM. Some of these new studies and analyses were conducted in response to the NRC (2011) comments and recommendations, while others reflect ongoing work and updates of studies on this topic. All add to the scientific evidence surrounding the potential causal relationship between formaldehyde inhalation exposure and LHM, and should be addressed in the critical evaluations and integration of evidence presented in an updated IRIS Assessment.

Also since the NRC (2011) peer review, the EPA has proposed enhancements to the IRIS process (EPA, 2013b) that incorporate many of the general recommendations made by the NRC (2011) related to methodological issues. This process involves the evaluation and synthesis of evidence within separate streams of evidence (human, animal and mechanistic). However, in a critical review of the process conducted by a separate NRC Committee, while there was improvement in guidelines for evaluation and synthesis of evidence within an

evidence stream, the NRC Committee still noted limitations in synthesizing or integrating evidence across streams or categories (NRC, 2014a).

Nearly all of the recently available evidence from multiple lines of evidence, especially those studies that have been focused on addressing comments from the NRC Committee reviewing the Draft IRIS Assessment (NRC, 2011), have increased the weight of evidence favoring a conclusion of a lack of a causal association between formaldehyde exposure and LHM. The Checkoway et al. (2015) re-analysis using the data from the Beane Freeman et al. (2009) study was able to address directly several questions and comments from the NRC (2011) Committee, as the Draft IRIS Assessment (2010) was highly dependent on this study for drawing both qualitative and quantitative conclusions related to formaldehyde leukemogenicity and risk of LHM following inhalation exposure to formaldehyde. The Checkoway et al. (2015) reanalysis provides several results and insights relevant for assessing the risk of specific LHM. Not the least of these, the AML-specific results provide no support for the conclusion that formaldehyde causes AML. Associations seen between formaldehyde exposure and Hodgkin lymphoma and CML are inconsistent with other studies and also lack a plausible biological mechanism (Checkoway et al., 2015). NTP (2011) also noted that because the evidence for Hodgkin lymphoma is mainly limited to the NCI cohort study, a causal association cannot be established. No other LHM was associated with either cumulative or peak formaldehyde exposure. These results of the fuller analysis of the data from Beane Freeman et al. (2009) are consistent with recent epidemiological studies (Meyers et al., 2013; Saberi Hosnijeh et al. 2013; Talibov et al., 2014) which report no significant increase in LHM, specifically AML, among cohorts of workers exposed to formaldehyde.

The available animal evidence did not support a causal association between formaldehyde exposure and LHM at the time the Draft IRIS Assessment (EPA, 2010) was released. Since that time, additional studies have been conducted by the NTP using two sensitive assays in mice genetically predisposed to develop cancer following short-term exposure to a chemical (Morgan et al., 2017). These studies provided no evidence of changes in endpoints related to LHM or the presence of any LHM following exposure to high concentrations (15 ppm) of formaldehyde.

Studies conducted to evaluate potential mechanisms associated with formaldehyde exposure and LHM have demonstrated a lack of evidence for exogenous formaldehyde to move beyond the portal of entry. Multiple studies conducted in multiple species using highly sensitive techniques (Edrissi et al., 2013; Lu et al., 2011; Moeller et al., 2011; Yu et al., 2015) have demonstrated that while endogenous formaldehyde is present in all tissues, exogenous formaldehyde following inhalation exposure is not transported systemically. While some mechanisms for the development of LHM following inhalation exposure to formaldehyde have been hypothesized (EPA, 2010; Zhang et al., 2009, 2010a), there is no evidence to support these proposed mechanisms and the NRC Committee noted that:

> "Although EPA postulated that formaldehyde could reach the bone marrow either as methanediol or as a byproduct of nonenzymatic reactions with glutathione, numerous studies described above have demonstrated that systemic delivery of formaldehyde is highly unlikely at concentrations below those which overwhelm metabolism according to sensitive and selective analytic methods that can differentiate endogenous from exogenous exposures." (NRC, 2011; page 45)

The more recent research all but confirms this. Several modes of action have been proposed, relying primarily on data reported by Zhang et al. (2010a) as well as subsequent evaluations of the same population of Chinese workers (Bassig et al., 2016; Lan et al., 2015; Seow et al., 2015). These include a mode of action in which risk of ML is increased due to immune suppression resulting from formaldehyde exposure (Bassig et al., 2016; Seow et al., 2015). The speculated modes of action, however, assume systemic delivery of formaldehyde except one, which is a hypothesized mode of action in which hematopoietic cells in the nasal epithelium that are impacted by exposure to formaldehyde return to the bone marrow. The NRC Committee considered this proposed mode of action and concluded that:

> "As a result, EPA could only speculate that circulating hematopoietic stem cells that percolate through nasal capillary beds or nasal-associated lymphoid tissues may be the target cells for mutations and clastogenic effects that eventually result in lymphohemotopoietic cancers. Experimental evidence of [this] mechanism is lacking." (NRC, 2011; page 45)

This currently leaves no acceptable proposed mode of action for the development of LHM following inhalation exposure to formaldehyde that can be scientifically substantiated.

The available toxicokinetic data also do not support the transport of inhaled formaldehyde from the portal of entry. The studies by Swenberg and colleagues unequivocally demonstrate that exogenous formaldehyde exposure does not increase formaldehyde concentrations measured in any internal tissues over those in unexposed animals, i.e., endogenously produced formaldehyde is the predominant if not only source of internal formaldehyde (Edrissi et al., 2013; Lu et al., 2010, 2011; Moeller et al., 2011; Swenberg et al., 2011; Yu et al., 2015).

The biological plausibility of a mode of action for the development of LHM following inhalation exposure to formaldehyde has relied heavily upon the incompletely reported results from the Zhang et al. (2010a) study in which the authors report differences between groups of formaldehyde exposed and unexposed groups in the frequency of monosomy 7 (loss of chromosome) and trisomy 8 (gain of chromosome), based on metaphase spreads prepared from culture of CFU-GM colony cells. However, reanalysis of the underlying raw data in two studies (Gentry et al., 2013; Mundt et al., 2017) have identified methodological problems with this study that challenge these conclusions, as well as demonstrate a lack of association between level of formaldehyde exposure and the observed aneuploidy (or any of the haematological measures).

Overall, the quality and amount of evidence relevant to the understanding of a potential causal relationship between formaldehyde inhalation exposure and risk of LHM has increased substantially since the completion of the Draft IRIS Assessment (EPA, 2010) and release of the NRC peer review (NRC, 2011). New evidence has been published in each of the major streams of evidence (i.e., human, animal and mechanistic) that consistently indicates a lack of a causal association between formaldehyde exposure and LHM, and specifically AML. These new studies have addressed many of the NRC (2011) scientific criticisms surrounding the evaluation of a combination of cancer types, as well as increased our understanding of the potential impact of exogenous exposure on endogenous levels, which is critical in attempting to understand the potential hazards or risks from formaldehyde exposure. Regardless of which of the several similar approaches to integrating the available evidence between formaldehyde inhalation exposure and the potential for leukemia risk, there is at most only limited suggestive positive evidence, in contrast with the bulk of evidence suggesting no such association. Therefore, a conclusion of causation is not justified scientifically. The scientific landscape into which EPA will release its long-anticipated revised *IRIS Toxicological Review of Formaldehyde – Inhalation Assessment* is very different from that of the 2010 Draft IRIS Assessment, both in terms of improved methodological approaches and the available epidemiological, toxicological and mechanistic evidence. Given formaldehyde's commercial importance, ubiquity in the environment and endogenous production, accurate determination of whether occupational, residential, or consumer exposure to formaldehyde causes leukemia or any type of human neoplasm is critical.

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Zhang, L., Ji, Z., Guo, W., Hubbard, A.E., Galvan, N., Xin, K.X., Azuma, M., Smith, M.T., Tang, X., Qiu, C., Ge, Y., Hua, M., Ruan, X., Li, S., Xie, Y., Li, L., Huang, H., Rothman, N., Shen, M., Beane Freeman, L., Blair, A., Alter, B.P., Moore, L.E., Hayes, R.B., Hauptmann, M., Stewart, P., Fraumeni Jr., J.F., Lan, Q., Vermeulen, R., Reiss, B., Liu, S., Xiong, J., Kim, S., Rappaport, S.M., 2010b. Occupational exposure to formaldehyde, hematotoxicity, and leukemia-specific chromosome changes in cultured myeloid progenitor cells: Response to Letter to Editor by Speit, et al.. Cancer Epidemiol. Biomarkers Prev. 19 (7), 1884–1885.
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Appointment

From: Bahadori, Tina [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=7DA7967DCAFB4C5BBC39C666FEE31EC3-BAHADORI, TINA]
Sent: 1/16/2018 8:17:46 PM
To: Mazza, Carl [Mazza.Carl@epa.gov]

Subject: FW: Meeting with ACC on Formaldehyde
Location: 41213 RRB/via video to B249

Start: 1/24/2018 7:00:00 PM
End: 1/24/2018 8:00:00 PM
Show Time As: Tentative

-----Original Appointment-----
From: Gentry, Nathan **On Behalf Of** Orme-Zavaleta, Jennifer
Sent: Tuesday, January 16, 2018 11:23 AM
To: Orme-Zavaleta, Jennifer; Rodan, Bruce; Yamada, Richard (Yujiro); Fleming, Megan; Christian, Megan; Kuhn, Kevin; Bahadori, Tina
Cc: Vandenberg, John; Thayer, Kris; Lavoie, Emma; Axelrad, Daniel; Ross, Mary; Bussard, David
Subject: Meeting with ACC on Formaldehyde
When: Wednesday, January 24, 2018 2:00 PM-3:00 PM (UTC-05:00) Eastern Time (US & Canada).
Where: 41213 RRB/via video to B249

From: White, Kimberly [mailto:Kimberly_White@americanchemistry.com]
Sent: Monday, December 04, 2017 8:22 AM
To: Orme-Zavaleta, Jennifer <Orme-Zavaleta.Jennifer@epa.gov>
Subject: Follow-up

Dear Dr. Orme-Zavaleta,

Thank you for your initial response to my November 21st letter. Do you have availability for a 1 hour meeting in Washington, DC sometime during the week of January 22nd to discuss further?

Separately, I also wanted to alert you to a recently published article by Mundt et al. titled "Six years after the NRC Review of EPA's Draft IRIS Toxicological Review of Formaldehyde: Regulatory implications of new science in evaluating formaldehyde leukemogenicity". I have appended a copy of the in press version to this email and excerpted the abstract below.

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Regul Toxicol Pharmacol. 2017 Nov 17. pii: S0273-2300(17)30363-X. doi: 10.1016/j.yrtph.2017.11.006. [Epub ahead of print]

Six years after the NRC Review of EPA's Draft IRIS Toxicological Review of Formaldehyde: Regulatory implications o f new science in evaluating formaldehyde leukemogenicity.

Mundt KA[1], Gentry PR[2], Dell LD[2], Rodricks JV[2], Boffetta P[3].
Author information
Abstract

Shortly after the International Agency for Research on Cancer (IARC) determined that formaldehyde causes leukemia, the United States Environmental Protection Agency (EPA) released its Draft IRIS Toxicological Review of Formaldehyde, also concluding that formaldehydecauses leukemia. Peer review of the EPA Draft IRIS Assessment by a National Academy of Science committee noted that "causal determinations are not supported by the narrative provided in the draft" {NRC 2011}. They offered recommendations for improving the IRISreview and identified several important research gaps. Over the six years since the NRC peer review, significant new science has been published. We identify and summarize key NRC recommendations and map them to this new science, including extended analysis of epidemiological studies, updates of earlier occupational cohort studies, toxicological experiments using a sensitive mouse strain, mechanistic studies examining the role of exogenous versus endogenous formaldehyde in bone marrow, and several critical reviews. With few exceptions, new findings are consistently negative, and integration of all available evidence challenges the earlier conclusions that formaldehyde causes leukemia. Given formaldehyde's commercial importance, environmental ubiquity and endogenous production, accurate hazard classification and risk evaluation of whether exposure to formaldehyde from occupational, residential and consumer products causes leukemia are critical.

KEYWORDS:

Epidemiology; Evidence integration; Hazard evaluation; Mechanistic studies; Regulatory science; Toxicology

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Kind Regards,

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Kimberly_White@americanchemistry.com
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Message

From: Bahadori, Tina [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=7DA7967DCAFB4C5BBC39C666FEE31EC3-BAHADORI, TINA]
Sent: 1/16/2018 8:15:52 PM
To: Gentry, Nathan [Gentry.Nathan@epa.gov]
Subject: RE: Meeting with ACC on Formaldehyde

Hi Nathan,
Can we add a video connection to RTP Room B-249 and a call-in number to this invite for folks calling in?
Thanks,
Tina

-----Original Appointment-----
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Appointment

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Sent: 1/16/2018 2:47:52 PM
To: Vandenberg, John [Vandenberg.John@epa.gov]; Thayer, Kris [thayer.kris@epa.gov]; Lavoie, Emma [Lavoie.Emma@epa.gov]; Axelrad, Daniel [Axelrad.Daniel@epa.gov]; Ross, Mary [Ross.Mary@epa.gov]; Bussard, David [Bussard.David@epa.gov]

Subject: FW: Meeting with ACC on Formaldehyde
Location: DCRoomRRB41213/ORD

Start: 1/24/2018 7:00:00 PM
End: 1/24/2018 8:00:00 PM
Show Time As: Tentative

-----Original Appointment-----
From: Orme-Zavaleta, Jennifer
Sent: Monday, December 4, 2017 1:55 PM
To: Orme-Zavaleta, Jennifer; Rodan, Bruce; Yamada, Richard (Yujiro); Fleming, Megan; Christian, Megan; Kuhn, Kevin; Bahadori, Tina
Subject: Meeting with ACC on Formaldehyde
When: Wednesday, January 24, 2018 2:00 PM-3:00 PM (UTC-05:00) Eastern Time (US & Canada).
Where: DCRoomRRB41213/ORD

From: White, Kimberly [mailto:Kimberly_White@americanchemistry.com]
Sent: Monday, December 04, 2017 8:22 AM
To: Orme-Zavaleta, Jennifer <Orme-Zavaleta.Jennifer@epa.gov>
Subject: Follow-up

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www.americanchemistry.com

Message

From: Walters, Brandon [Walters.Brandon@epa.gov]
Sent: 1/24/2018 12:35:28 PM
To: Bennett, John [Bennett.John@epa.gov]; Blancato, Jerry [Blancato.Jerry@epa.gov]; Cunningham, Denise [Cunningham.Denise@epa.gov]; Gonzalez, Michael [Gonzalez.Michael@epa.gov]; Gundlach, Mary [Gundlach.Mary@epa.gov]; Gutierrez, Sally [Gutierrez.Sally@epa.gov]; Hubbard, Carolyn [Hubbard.Carolyn@epa.gov]; Kasper, Sandy [Kasper.Sandy@epa.gov]; Kleinman, Brian [Kleinman.Brian@epa.gov]; Matchen, Irving [Matchen.Irving@epa.gov]; Mayes, Desmond [Mayes.Desmond@epa.gov]; Orme-Zavaleta, Jennifer [Orme-Zavaleta.Jennifer@epa.gov]; Quinn, Karen [Quinn.Karen@epa.gov]; Teichman, Kevin [Teichman.Kevin@epa.gov]; vanDrunick, Suzanne [vanDrunick.Suzanne@epa.gov]; Watkins, Tim [Watkins.Tim@epa.gov]; Frithsen, Jeff [Frithsen.Jeff@epa.gov]; Thomas, Sheryl [Thomas.Sheryl@epa.gov]; D'Amico, Louis [DAmico.Louis@epa.gov]; Hauchman, Fred [hauchman.fred@epa.gov]; Steenbock, John [Steenbock.John@epa.gov]; Andrew, Karen [Andrew.Karen@epa.gov]; Troyer, Michael [Troyer.Michael@epa.gov]; Blackburn, Elizabeth [Blackburn.Elizabeth@epa.gov]; Sayles, Gregory [Sayles.Gregory@epa.gov]; Ifediora, Byron [Ifediora.Byron@epa.gov]; Robbins, Chris [Robbins.Chris@epa.gov]; Heckman, Deborah [Heckman.Deborah@epa.gov]; Greene, Mary [greene.mary@epa.gov]; Perry, Dale [Perry.Dale@epa.gov]; McPherson, Mark [McPherson.Mark@epa.gov]; Rodan, Bruce [rodan.bruce@epa.gov]; Silzer, Stefan [Silzer.Stefan@epa.gov]; Bahadori, Tina [Bahadori.Tina@epa.gov]; Yamada, Richard (Yujiro) [yamada.richard@epa.gov]; Thomas, Sheryl [Thomas.Sheryl@epa.gov]; Updike, David [Updike.David@epa.gov]; Wright, Linda [Wright.Linda@epa.gov]; Gray, Barbara [Gray.Barbara@epa.gov]; Holt, Kay [Holt.Kay@epa.gov]; Cascio, Wayne [Cascio.Wayne@epa.gov]; Branch, Danielle [branch.danielle@epa.gov]; Christian, Megan [Christian.Megan@epa.gov]; Fleming, Megan [Fleming.Megan@epa.gov]; Kuhn, Kevin [Kuhn.Kevin@epa.gov]; Tun, Amanda [tun.amanda@epa.gov]; Weber, Luke [Weber.Luke@epa.gov]
Subject: Daily Calendar January 24, 2018
Attachments: Daily Calendar January 24.pdf

Brandon Walters
U.S. EPA Office of Research and Development
Immediate Office of the Assistant Administrator
202.564.1662 | walters.brandon@epa.gov

Appointment

From: Thayer, Kris [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=3CE4AE3F107749C6815F243260DF98C3-THAYER, KRI]
Sent: 1/16/2018 6:29:11 PM
To: Orme-Zavaleta, Jennifer [Orme-Zavaleta.Jennifer@epa.gov]

Subject: Accepted: Meeting with ACC on Formaldehyde
Location: 41213 RRB/via video to B249

Start: 1/24/2018 7:00:00 PM
End: 1/24/2018 8:00:00 PM
Show Time As: Busy

Appointment

From: Vandenberg, John [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=DCAE2B98A04540FB8D099F9D4DEAD690-VANDENBERG, JOHN]
Sent: 1/16/2018 12:52:00 PM
To: Vandenberg, John [Vandenberg.John@epa.gov]

Subject: Formaldehyde meeting with ACC

Start: 1/24/2018 7:00:00 PM
End: 1/24/2018 8:00:00 PM
Show Time As: Busy

Orme-Zavaleta, Jennifer
Sent: Monday, December 4, 2017 1:55 PM
To: Orme-Zavaleta, Jennifer; Rodan, Bruce; Yamada, Richard (Yujiro); Fleming, Megan; Christian, Megan; Kuhn, Kevin; Bahadori, Tina
Subject: Meeting with ACC on Formaldehyde
When: Wednesday, January 24, 2018 2:00 PM-3:00 PM (UTC-05:00) Eastern Time (US & Canada).
Where: DCRoomRRB41213/ORD

Appointment

From: Vandenberg, John [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=DCAE2B98A04540FB8D099F9D4DEAD690-VANDENBERG, JOHN]
Sent: 1/16/2018 4:12:06 PM
To: Orme-Zavaleta, Jennifer [Orme-Zavaleta.Jennifer@epa.gov]

Subject: Accepted: FW: Meeting with ACC on Formaldehyde
Location: DCRoomRRB41213/ORD

Start: 1/24/2018 7:00:00 PM
End: 1/24/2018 8:00:00 PM
Show Time As: Busy

Message

From: Yeow, Aaron [Yeow.Aaron@epa.gov]
Sent: 5/1/2018 11:57:12 AM
To: AO SAB EVERYONE [AO_SAB_EVERYONE@epa.gov]
Subject: Climatewire - How Pruitt's science plans might help industry fight rules

EPA

How Pruitt's science plans might help industry fight rules

Scott Waldman, E&E News reporter

Published: Tuesday, May 1, 2018

Dozens of prominent scientists published an alarming study about formaldehyde in 2010. Their findings: Exposure to the compound — used in everything from auto manufacturing to embalming — was linked to leukemia.

It's the type of study that can significantly influence major public health regulations. The research, published in the journal *Cancer Epidemiology, Biomarkers & Prevention*, has made waves in the public health world. It's been cited by both EPA and the International Agency for Research on Cancer in assessments that linked formaldehyde to leukemia and other serious health problems.

Now, the study long fought by industry is being cited as an example of the kind of public health research EPA Administrator Scott Pruitt and his allies could soon keep out of the rulemaking process. And controversy over the paper could offer a glimpse into how industry might use changes to EPA's science policies to try to discredit some public health research that bolsters the case for regulations.

Pruitt last week proposed a rule to require that EPA studies used in future regulations must have open and transparent data. Pruitt and other conservatives have argued that EPA's current process is too opaque and allows government officials to push their own regulatory agendas without having the data to back up their decisions.

Pruitt said that his plan will give the "marketplace" a way to evaluate science used in rulemaking. His new policy, he said, is designed to utilize "common sense that as we do rulemaking at the agency, we base it upon a record, scientific conclusions, that we should be able to see the data and methodology that actually caused those conclusions."

His opponents say Pruitt's plan opens the door for industry to go after a range of important studies that underpin public health protections and climate change regulations. A fight over the formaldehyde research might offer a window into how it will play out.

The formaldehyde and leukemia study is a "poster child" for the way industry could attempt to tear down important research that threatens their profits, said Bernard Goldstein, dean emeritus of the University of Pittsburgh Graduate School of Public Health, who was EPA's top science official during the Reagan administration.

The study examined health data of factory workers in China exposed to formaldehyde and concluded that "leukemia induction by formaldehyde is biologically plausible." The authors included researchers from the University of California, Berkeley; the National Cancer Institute; and the U.S. Department of Health and Human Services as well as Chinese institutions. Researchers kept the underlying data private, citing health confidentiality concerns.

Counter by chemicals industry

The chemicals industry — which could see its bottom line affected by formaldehyde rules — took aim at that research immediately after it was published in 2010.

The American Chemistry Council, a trade group for the industry, fought for years in court to receive the underlying data behind the study, according to a timeline provided by the organization. Because some of the researchers worked for government agencies, industry researchers were able to use a Freedom of Information Act request to obtain some of the underlying data.

After the organization received the data from the original study, in 2016, it quickly turned it around into a reanalysis it used to claim the original study was invalid.

The resulting 2017 study funded by a foundation attached to the American Chemistry Council found "little if any evidence of a causal association between formaldehyde exposure and AML (acute myelogenous leukemia)." The study was published in the journal *Critical Reviews in Toxicology*, which has been criticized by the Center for Public Integrity because it routinely publishes industry-funded work used to fight regulations.

In a press release announcing the study, the American Chemistry Council argued that the research published in 2017 invalidated not only the original study but also all of the regulations it may have supported.

"The findings in this reanalysis are important because they call into question the validity of all these recent formaldehyde assessments," Kimberly White, senior director of the American Chemistry Council Formaldehyde Panel, said in the press release last year. "The original paper failed to meet its own data quality standards and the scientific standard of reproducibility. Relying on it consequently led to unsubstantiated regulatory decisions and unwarranted outcomes."

The trade group told E&E News in a statement yesterday: "Formaldehyde is an extensively regulated material. EPA and other agencies must consider the entire weight of evidence on formaldehyde, as is the case for all chemicals, when setting exposure limits."

Former officials from the powerful trade group now hold top political posts at EPA under Pruitt.

And White is now a member of EPA's influential Science Advisory Board tasked with evaluating research used to craft regulations. She was appointed after Pruitt reworked the board, declaring that members who received EPA grants could no longer serve. Critics of that move argued that the shift tipped the scales toward researchers with industry ties, because many academics rely on federal grant funding.

'What is solid science?'

Goldstein, the former Reagan-era EPA official, sees the fight over the formaldehyde research as a preview of how Pruitt's plans will affect EPA science.

"You hear this from the American Chemistry Council over and over again saying, 'See, we were finally able to get the data through the Freedom of Information Act and it turns out these folks were hiding things which

completely contradict their findings,' which is just nonsense," he said. "They found a private consultant group that was able to look at the data in such a way as to give them the opportunity to say that even though it was not justified."

Goldstein said there's been a decadeslong trend where industry looks to exploit minor flaws to delegitimize important research. Any study with such significant ramifications for human health will often yield further independent research that will fully explore and vet such flaws, he added.

He accused the American Chemistry Council of waging a political and legal war, rather than focusing on research.

"Instead of funding new science to see whether this thing is right or wrong — because one study is never going to be definitive — what you're going to do is you're going to give the money to people to find minor blemishes, which are inevitable when you do these kinds of studies, and you're going to fight it out in courts, not in science," Goldstein said.

Supporters of Pruitt's proposed rule say it will allow for independent analysis of research that informs costly regulations.

At contentious hearings on Capitol Hill last week, a number of House Republicans hailed the science transparency rule as progress.

"The question is, what is solid science?" said Rep. Mike Simpson (R-Idaho). He shrugged off criticisms of EPA's proposal. "I can't believe anybody has a problem with [asking], 'How did you come up with this conclusion?'"

Offering more raw data, however, could allow industry to take data out of context and to rework it with predetermined findings that it will claim invalidates the work of established and independent researchers, Goldstein said. He said industry has a long history of hiring its own researchers to nitpick and rebut data.

"You're a great consultant for industry if you can find a way to give industry, your client, an argument that will allow them to win a case whether or not your argument is scientifically valid," he said. "It's a matter of we're taking the science and changing it into a legal approach, a confrontational approach, rather the consensus approach. And industry and Scott Pruitt are rather happy to have a confrontational approach because they're in charge now."

Message

From: Bahadori, Tina [Bahadori.Tina@epa.gov]
Sent: 6/18/2018 3:15:21 PM
To: Carpenter, Thomas [Carpenter.Thomas@epa.gov]
CC: Thayer, Kris [thayer.kris@epa.gov]; Brennan, Thomas [Brennan.Thomas@epa.gov]; Johnston, Khanna [Johnston.Khanna@epa.gov]; Shallal, Suhair [Shallal.Suhair@epa.gov]; Bright, Wanda [Bright.Wanda@epa.gov]
Subject: RE: Kimberly Wise White

OK, thanks for the clarification, Tom. I will go ahead and respond then.
TIna

From: Carpenter, Thomas
Sent: Monday, June 18, 2018 10:15 AM
To: Bahadori, Tina <Bahadori.Tina@epa.gov>
Cc: Thayer, Kris <thayer.kris@epa.gov>; Brennan, Thomas <Brennan.Thomas@epa.gov>; Johnston, Khanna <Johnston.Khanna@epa.gov>; Shallal, Suhair <Shallal.Suhair@epa.gov>; Bright, Wanda <Bright.Wanda@epa.gov>
Subject: RE: Kimberly Wise White

Hello Tina,
Thank you for letting us know. The SAB is not currently reviewing a formaldehyde assessment. Dr. White is providing comments as part of her responsibilities at ACC. Special government employees are not precluded from their employment duties when they serve on federal advisory committees Consistent with the ethics training we have provided, should the SAB engage in a review of formaldehyde, she should declare, in the supplemental ethics questions, she is the signee of an ACC comment regarding formaldehyde. The SAB staff Office then considers whether the letter presents any issues of loss of impartiality, objectivity or balance of the SAB regarding her participation in such a review. These issues are not conflict of interest (COI) which are codified as financial COI.

Best
Tom

From: Bahadori, Tina
Sent: Friday, June 15, 2018 8:00 PM
To: Carpenter, Thomas <Carpenter.Thomas@epa.gov>
Cc: Thayer, Kris <thayer.kris@epa.gov>
Subject: Kimberly Wise White

Hi Tom,
Before I respond to this communication by Dr. Wise White, I wanted to make sure this was not a COI issue from the perspective of SAB?
Thanks,
Tina

From: White, Kimberly [mailto:Kimberly_White@americanchemistry.com]
Sent: Friday, June 15, 2018 1:03 PM
To: Bahadori, Tina <Bahadori.Tina@epa.gov>
Cc: Thayer, Kris <thayer.kris@epa.gov>; Orme-Zavaleta, Jennifer <Orme-Zavaleta.Jennifer@epa.gov>; Yamada, Richard (Yujiro) <yamada.richard@epa.gov>
Subject: Letter Highlighting New Commentary Submitted on Behalf of the ACC Formaldehyde Panel

Dear Dr. Bahadori:

Please find attached a letter submitted on behalf of the American Chemistry Council's Formaldehyde Panel, highlighting a recently published commentary.

Kind Regards,

Kimberly Wise White, Ph.D. | American Chemistry Council
Senior Director, Chemical Products & Technology Division
Kimberly_White@americanchemistry.com
700 2nd Street NE | Washington, DC | 20002
O: (202) 249-6707 C: (202) 341-7602
www.americanchemistry.com

Message

From: Bahadori, Tina [Bahadori.Tina@epa.gov]
Sent: 6/16/2018 12:00:11 AM
To: Carpenter, Thomas [Carpenter.Thomas@epa.gov]
CC: Thayer, Kris [thayer.kris@epa.gov]
Subject: Kimberly Wise White
Attachments: ACC Formaldehyde Panel Letter to EPA on Thompson 2018 Commentary - 06 15 18.pdf; Attachment 1 - Thompson Commentary on Formaldehyde NTP Study - June 2018.pdf

Hi Tom,
Before I respond to this communication by Dr. Wise White, I wanted to make sure this was not a COI issue from the perspective of SAB?
Thanks,
Tina

From: White, Kimberly [mailto:Kimberly_White@americanchemistry.com]
Sent: Friday, June 15, 2018 1:03 PM
To: Bahadori, Tina <Bahadori.Tina@epa.gov>
Cc: Thayer, Kris <thayer.kris@epa.gov>; Orme-Zavaleta, Jennifer <Orme-Zavaleta.Jennifer@epa.gov>; Yamada, Richard (Yujiro) <yamada.richard@epa.gov>
Subject: Letter Highlighting New Commentary Submitted on Behalf of the ACC Formaldehyde Panel

Dear Dr. Bahadori:

Please find attached a letter submitted on behalf of the American Chemistry Council's Formaldehyde Panel, highlighting a recently published commentary.

Kind Regards,

Kimberly Wise White, Ph.D. | American Chemistry Council
Senior Director, Chemical Products & Technology Division
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June 15, 2018

Dr. Tina Bahadori
Director, NCEA
USEPA Headquarters
Ariel Rios Building
1200 Pennsylvania Avenue, N. W.
Mail Code: 8601P
Washington, DC 20460

Re: 2018 Commentary on New Formaldehyde Studies in Trp53 Haploinsufficient Mice: Further Support for Nonlinear Risks From Inhaled Formaldehyde

Dear Dr. Bahadori:

I am writing to call to your attention a June 2018 article by C. Thompson titled: "Commentary on New Formaldehyde Studies in Trp53 Haploinsufficient Mice: Further Support for Nonlinear Risks From Inhaled Formaldehyde." The article discusses the relevance of a 2017 final report by the U. S. National Toxicology Program (NTP) that explored the potential involvement of p53 mutation in formaldehyde-induced nasal tumors and lymphohematopoietic cancers. The NTP study demonstrated that inhalation of a maximum tolerated dose of formaldehyde did not cause nasal tumors, did not cause an increased prevalence of leukemia or lymphohematopoietic cancer, and did not cause any other type of cancer in $Trp53^{+/-}$ mice. It provides additional support for utilizing a non-linear threshold model for the dose-response analysis of formaldehyde.

The commentary reinforces that the mode of action of inhaled formaldehyde must be foundational for characterizing the hazard and dose-response assessment. The 2017 NTP report adds to the overall weight of the evidence illustrating that inhaled formaldehyde is not leukemogenic. The 2017 NTP report is consistent with results from available mode of action studies demonstrating that nasal tumors observed in rodent studies following inhalation exposure to formaldehyde are limited to the nasopharyngeal region and are only associated with exposure to high concentrations of formaldehyde. Moreover, the 2017 NTP report lends further support that formaldehyde-induced nasal tumors are highly unlikely to be caused via a mutagenic mode of action as is typically assumed in linear dose-response modeling for cancer assessments.

Consideration of mode of action information is critical in establishing the biological plausibility of carcinogenicity and understanding how inhalation of formaldehyde may impact normal physiological levels and processes. The 2011 NAS report[1] called for selecting outcomes on the basis of available evidence and an understanding of mode of action. The application and integration of this information is essential to reduce uncertainty in characterizing potential human health risk from formaldehyde exposures and its importance cannot be overstated. The

[1] National Academy of Sciences (NAS). National Research Council (NRC). 2011. Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde. Committee to Review EPA's Draft IRIS Assessment of Formaldehyde. Board of Environmental Studies and Toxicology. Division of Earth and Life Sciences.

Panel continues to urge the Agency to apply mode of action research as the foundation for a scientifically defensible hazard characterization and dose-response analysis for formaldehyde.

Feel free to contact me by phone (202-249-6707) or email (Kimberly_White@americanchemistry.com) with any questions related to this letter. Additionally, a full copy of the commentary is attached for your reference.

Sincerely,

Kimberly Wise White, PhD
American Chemistry Council (ACC)
Senior Director
Chemical Products & Technology Division
On Behalf of the ACC Formaldehyde Panel

Cc:
Kris Thayer, Director of the Integrated Risk Information System Division
Richard Yamada, Deputy Assistant Administrator for the Office of Research and Development.
Jennifer Orme-Zavaleta, Principal Deputy Assistant Administrator for Science for the Office of Research and Development, and EPA Science Advisor

Attachment 1 – Thompson, C. M. (2018). Commentary on New Formaldehyde Studies in Trp53 Haploinsufficient Mice: Further Support for Nonlinear Risks From Inhaled Formaldehyde. Dose-Response, 16(2), 1559325818777931.

Dose-Response:
An International Journal
April-June 2018:1-2

DOI: 10.1177/1559325818777931
journals.sagepub.com/home/dos
SAGE

Commentary on New Formaldehyde Studies in Trp53 Haploinsufficient Mice: Further Support for Nonlinear Risks From Inhaled Formaldehyde

Chad M. Thompson[1]

Keywords
dose–response, risk assessment, formaldehyde, mode of action

Commentary

Formaldehyde is a widely used industrial chemical, a byproduct of combustion, and is generated endogenously. Although classified by many organizations as a carcinogen, the World Health Organization (WHO) has set an exposure guideline of 0.08 ppm based on irritant properties of formaldehyde.[1] The US Environmental Protection Agency has proposed far lower safety values based, in part, on controversial associations between formaldehyde exposure and increased risk of leukemia. Therefore, it is of interest that the National Toxicology Program (NTP), a division of the National Institute of Environmental Health Sciences, recently released an NTP Research Report that explored the potential involvement of p53 mutation in formaldehyde-induced nasal tumors as well as lymphohematopoietic cancers.[2] This study has not been published in the peer-review literature, nor is the report currently indexed in search engines like PubMed and Embase. Because the carcinogenicity of formaldehyde remains controversial and there are ongoing assessments of formaldehyde in the United States, the new NTP Research Report is an important addition to the database for informing the carcinogenicity of inhaled formaldehyde. This commentary highlights some important implications of this study for the risk assessment of formaldehyde.

In the new NTP Research Report, 2 mouse strains (note 1) haploinsufficient for TP53 were exposed to 7.5 and 15 ppm formaldehyde for 8 weeks and killed 32 weeks later at $\sim$50 weeks of age.[2] At termination, the NTP Research Report indicates that neither hematotoxicity nor lymphohematopoietic neoplasms were observed in either strain.[2] *Tp53*$^{+/-}$ mice were designed such that shortened cancer bioassays could be conducted due to their increased sensitivity to carcinogens—particularly genotoxic carcinogens.[3] These mouse strains are also reported to develop spontaneous lymphomas[3] and serve as models for lymphohematopoietic tumors in short-term studies.[2] These findings lend additional weight to the evidence that inhaled formaldehyde is not leukemogenic—including reanalysis of epidemiological studies[4] and animal studies that indicate that inhaled formaldehyde does not distribute beyond the nasal cavity or reach the blood or bone marrow.[5]

The new NTP Research Report also provides important insight into the mode of action (MOA) for nasal tumors in rodents. Formaldehyde-induced nasal tumor formation is well-documented in rats at $\geq$6 ppm,[6] and research indicates that tumors arise in nasal regions where there is cytotoxicity and regenerative hyperplasia. Research into the MOA for nasal tumors led to the development of one of the few biologically based dose–response (BBDR) models ever developed for use in risk assessment. The BBDR model and supporting research indicate that the tumor response in rats is most likely driven by increased cytotoxicity-induced regenerative hyperplasia with a negligible contribution from direct mutagenicity at noncytotoxic concentrations.[7] Subsequent in vivo genotoxicity studies have shown that exposure to up to 15 ppm for several weeks increases cell proliferation but not micronuclei or mutant frequency of *kras* or *Tp53* in the nasal cavity.[8,9] These data indicate a negligible contribution from direct mutagenicity at cytotoxic concentrations. The lack of nasal neoplasms in *Tp53*$^{+/-}$ mice considered well suited for detecting genotoxic carcinogens lends additional evidence that the MOA for

[1] ToxStrategies, Inc., Katy, TX, USA

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formaldehyde-induced nasal tumors is unlikely to be a mutagenic MOA, as typically defined for cancer risk assessment. Importantly, the NTP study authors state that, "The primary formaldehyde-related finding was squamous metaplasia of the respiratory epithelium of the nose..." indicating that "...formaldehyde caused significant injury to the nasal mucosa and cell proliferation..."[2(pvi)] These observations weaken any counterargument that the exposures were too low or too short to have potentially induced nasal tumors.

Some scientists have argued that formaldehyde induces nasal tumors via a mutagenic MOA, citing evidence for labeled DNA-protein cross-links and DNA adducts in nasal tissue following inhalation of isotope labeled formaldehyde, in vitro evidence of genotoxicity, and variable evidence for genotoxicity in exfoliated nasal and buccal cells as well as lymphocytes of humans occupationally exposed to formaldehyde. Additionally, recent studies demonstrate that *endogenous* formaldehyde is genotoxic in mice genetically engineered to be susceptible to formaldehyde due to increased production, decreased detoxification, compromised DNA repair, or some combination thereof.[10] However, as Speit et al[8] have noted, the absence of genotoxicity in nasal tissue of rats following inhalation exposure suggests that inhaled formaldehyde does not readily reach basal cells lining the nasal mucosa or that formaldehyde-induced DNA adducts and cross-links are readily repaired. The lack of nasal neoplasms in $Tp53^{+/-}$ mice seems consistent with this view.

In a vacuum, the new NTP Research Report does not exclude the possibility of a mutagenic MOA for nasal tumors. However, considered along with the broader in vivo data on formaldehyde, the weight of evidence supports the use of nonlinear approaches for estimating risks from exposure to environmental levels of formaldehyde. Indeed, the WHO argues that protection against the irritant effects of inhaled formaldehyde is protective against more severe effects such as cancer.[1] The new government-funded research in $Tp53^{+/-}$ mice further supports the argument that noncytotoxic concentrations of formaldehyde pose little/no carcinogenic risk. These important new findings should be considered by regulatory agencies currently assessing the carcinogenic risk of inhaled formaldehyde.

Note

1. C3B6.129F1-Trp53^{tm1Brd} and B6.129-Trp53^{tm1Brd}.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. Consulting fees received for writing might be perceived by some as a conflict.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was funded by the American Chemistry Council.

References

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2. Morgan DL, Dixon D, King DH, et al. NTP research report on absence of formaldehyde-induced neoplasia in trp53 haploinsufficient mice exposed by inhalation. *National Toxicology Program*. 2017;3:1-30.
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Senate Committee on Environment and Public Works
"Oversight Hearing to Receive Testimony from Environmental Protection Agency Administrator Scott Pruitt"
Questions for the Record for Administrator Scott Pruitt
January 30, 2018

Chairman Barrasso:

1. ***OAR:*** At the beginning of this Administration, prior to your confirmation, EPA alleged that Wyoming contributed to ozone problems in Douglas County, Colorado under the 2008 ozone National Ambient Air Quality Standards (NAAQS). To reach this conclusion, EPA applied a methodology designed for Eastern states.

   Western states have different topographies, higher altitudes, and different weather patterns than Eastern states. In addition, Western states have higher frequencies of wildfires than the East. Under EPA's "one-size-fits-all" model, EPA projected that a tiny amount of emissions would move from Wyoming to Colorado. EPA then imposed additional regulatory burdens on Wyoming. I raised my serious concerns and objections to EPA's action in a recent letter to you on January 19, 2018 (attached).

   In your oral testimony, you stated that EPA is evaluating challenges with international air transport. In a February 1, 2018 response to my letter from Bill Wehrum, Assistant Administrator for the Office of Air and Radiation (attached), he stated EPA plans to work with states "early this year to provide more information and flexibility as [states] look to address interstate transport issues under the 2015 ozone NAAQS." Will EPA also address any remaining interstate transport issues concerning other NAAQS, including the 2008 ozone NAAQS issue identified in my letter? If so, do you have an anticipated timeline for addressing these issues?

2. ***OAR:*** During the hearing, I asked you about 46 outstanding exceptional events filings from the State of Wyoming that EPA has yet to act on. As I mentioned during the hearing, I expressed my concern with EPA's decision not to act on these filings in 2016. Do you have a date by which EPA anticipates it will act on Wyoming's 46 petitions that I highlighted?

3. ***OW:*** As you know, the U.S. Army Corps of Engineers is the agency that makes the vast majority of jurisdictional determinations to identify waters that are regulated under the Clean Water Act. However, according to testimony before this Committee on April 26, 2017, the Corps was not included fully in the process of developing the 2015 Waters of the U.S. (WOTUS) rule.

   In fact, the Corps did not believe that the rule and preamble, as ultimately finalized, "were viable from a factual, scientific, analytical, or legal basis" and "it would be incredibly difficult for Corps leaders, regulatory and legal staff to advance and defend this rule…."

How will you ensure adequate coordination occurs between the EPA and Corps of Engineers in developing future regulations to delineate the jurisdiction of the Clean Water Act?

4. ***OAR:*** Last year, this Committee heard testimony about barriers under the Clean Air Act to the adoption of technologies that would reduce emissions and/or improve efficiency at power plants and other industrial facilities. Witnesses repeatedly stated that the New Source Review (NSR) program discouraged such projects. I am encouraged that both you and Bill Wehrum, Assistant Administrator for the Office of Air and Radiation, have identified NSR reform as a top priority for the Agency.

   What can this Committee – and Congress as a whole – do to assist you in these efforts and develop bipartisan support for reforms moving forward?

5. ***OW:*** Last year, Congress passed the bipartisan Water Infrastructure for Improvements to the Nation (WIIN) Act. On September 14, 2017, EPA granted petitions to reconsider a final rule that regulates coal combustion residuals (CCR) as nonhazardous waste under the Resource Conservation and Recovery Act (RCRA). You stated the purpose of reconsideration is as follows: "In light of EPA's new statutory authority [under the WIIN Act], it is important that we give the existing rule a hard look and consider improvements that may help states tailor their permit programs to the needs of their states, in a way that provides greater regulatory certainty, while also ensuring that human health and the environment remain protected."

   I support EPA's commitment to assure that the CCR rule provides adequate flexibility and authority to states. Does EPA have an anticipated timeline for completing this reconsideration so that states and regulated entities have maximum flexibility and regulatory certainty as soon as possible?

6. ***OAR:*** Over the last several years, increased efficiency of gas fueled vehicles and relatively low gas prices have led to fewer than projected consumer purchases of electric vehicles relative to gas fueled vehicles. Current data show how gas prices have been lower than projected in 2012 when vehicle standards were established by EPA and the Department of Transportation's (DOT) National Highway Traffic Safety Administration (NHTSA).

   In 2012, EPA issued standards for light-duty vehicles for MY 2017-2025, and committed to conduct a Midterm Evaluation (MTE) by April 1, 2018. I applaud the EPA's decision last year to reconsider the evaluation issued at the end of the last administration, which was issued under a rushed timeline and without adequate coordination with NHTSA. As you complete the MTE, will you commit to use the best available, current data and collaborate with NHTSA?

7. ***OAR:*** In 2016, the U.S. imported roughly 700 million gallons of biodiesel. Last year, EPA considered reducing the renewable fuel volume obligations (RVOs) for biomass-based diesel (BBD) for 2018 and 2019. EPA explained that it "could consider the

availability of imports as one factor among others in determining whether to exercise its discretion to use the waiver authority." About the same time, the U.S. International Trade Commission imposed tariffs on imported biodiesel from Argentina and Indonesia. Imports of biodiesel from these two nations declined in 2017 and may decline further this year.

a. How did EPA account for this foreseeable decrease in the supply of imported biodiesel when it set the 2019 RVOs for BBD?
b. If U.S. BBD production does not materially increase in 2018, is EPA prepared to reduce the 2020 RVOs for BBD below 2019 levels? If not, why not?
c. How does relying on imported biodiesel advance the Renewable Fuel Standard's purported objective of improving U.S. energy security?

8. ***OLEM:*** On December 23, 2016, GE submitted a completion report showing that it had completed implementation of EPA's plan for the cleanup of PCBs from the Hudson River. At that time, GE asked EPA to certify that the project is complete,[1] in accordance with a 2005 Consent Decree signed by GE and the EPA.[2] In that Consent Decree, EPA agreed to grant a certification of completion within 1 year of GE's submission of the completion report.[3] That has since passed, but to date the agency has yet to make a decision on the certificate of completion. When do you expect the agency to make a decision on the certificate of completion?

9. ***ORD:*** In December 2017, EPA announced "a cross-agency effort to address per and polyfluoroalkyl substances (PFAS)."

a. Is EPA collaborating with other federal agencies, state agencies, or other stakeholders on this initiative? If so, how are these entities contributing to EPA's cross-agency effort?
b. Will EPA provide the public with updates on EPA's progress and an opportunity to comment on EPA's work? If so, when do you anticipate this taking place?
c. How will EPA's cross-agency effort help inform ongoing and future state and local efforts to address PFAS?

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[1] "EPA is currently reviewing GE's Remedial Action Completion Report, which the company submitted to EPA, the federal natural resource trustees and New York State in December 2016." Proposed Second Five Year Review Report (2017) at pg. 20 (https://www.epa.gov/sites/production/files/2017-06/documents/hudson_second_five-year_review_report.pdf)

[2] See Consent Decree (https://www3.epa.gov/hudson/consent_decree/consent_decree.pdf)

[3] Consent Decree (Pgs. 40-41): paragraph 57.b (GE GE "shall submit to EPA, for review and approval, a Remedial Action Report . . . request[ing] EPA's Certification of Completion of the Remedial Action"); 57.d ("If EPA concludes . . . that the Remedial Action has been performed in accordance with this Consent Decree, EPA will so certify in writing"); 57.e ("EPA will respond to such request [for Certification] no later than 365 days after EPA's receipt of the request")

Ranking Member Carper:

10. ***ORD:*** EPA's February 1, 2018 Report to Congress on the Integrated Risk Information System (IRIS) states that EPA has already contracted with the National Academy of Sciences for peer review of the formaldehyde human health assessment.
    a. I have been informed that the human health assessment for formaldehyde was completed by IRIS staff months ago. Is that accurate?
    b. If so, why has the health assessment not yet been released i) for intra-agency review, ii) inter-agency peer review, iii) for public comment and iv) to the NAS for peer review, and when will each such step occur?
    c. If not, please describe precisely what work remains to be completed before each step described above can occur, along with time estimates for each step.
    d. Please provide me with an un-redacted copy of the current draft of the IRIS human health assessment for formaldehyde.

11. ***ORD:*** From January 20, 2017 until the present, please provide information regarding all meetings (including conference calls) related to the formaldehyde human health assessment, including the date, attendee names (and for non-EPA employees, their affiliations) and copies of any materials prepared for or obtained from each such meeting. Please also provide the same information for meetings EPA staff may have attended related to formaldehyde more generally.

12. ***ORD:*** The Report to Congress states that the IRIS staff have operationalized the "systematic review" process used to determine which and how scientific studies can be relied upon to inform IRIS assessments.
    a. Please provide me with a copy of the document that captures these revisions.
    b. OCSPP: Please additionally provide a copy of the document that describes the EPA Office of Chemical Safety and Pollution Prevention "fit for purpose" systematic review process that is referenced on page 19 of the December 12, 2017 EPA document entitled "Revised Glyphosate Issue Paper: Evaluation of Carcinogenic Potential[4]."

13. ***ORD:*** Please describe the timeline and full scope of the NAS review of the IRIS program described in the Report to Congress. Will the IRIS program's new "systematic review" process be included in the scope, and if not, why not?

14. ***OCSPP:*** When Congress was negotiating the final text of the Toxic Substances Control Act (TSCA), EPA came to Congress and asked for specific provisions that would allow the agency to move forward with bans for some uses of three highly toxic chemicals. Congress agreed, and that language was included in the final law. One of those chemicals, a paint stripper called methylene chloride, is so dangerous that it has killed dozens of people, even when they were wearing protective gear. EPA proposed rules banning these chemicals more than a year ago. But more recent reports indicate that EPA

[4] https://www.epa.gov/sites/production/files/2017-12/documents/revised_glyphosate_issue_paper_evaluation_of_carcinogenic_potential.pdf

may delay action on the uses of these chemicals for several more years, which almost certainly will mean that more people will get sick and probably some of them will die. When I asked you during the hearing whether you would commit to finalizing these bans within thirty days, you stated that "It's my understanding that is actually on the priority list as far as the chemicals that are we reviewing. TCE and others. So that is something that I will clarify and confirm with the agency. But that was my understanding." I believe you may have been referring to the *remaining* uses of these chemicals (i.e.the uses of the chemicals that are not covered by the proposed bans), which are on EPA's priority list for the first ten chemicals slated for review under TSCA. I was referring to the uses of these chemicals that EPA has *already* proposed to ban. Please provide the specific dates by which each of these proposed bans will be finalized.

15. ***OEI:*** According to the Paperwork Reduction Act, 44 USC § 3506(d)(3), all agencies must provide "adequate notice" when "substantially modifying, or terminating significant information dissemination products." On April 28, 2017, EPA removed the vast majority – thousands of pages – of its climate change websites, and it appears that EPA did not provide the public an opportunity to comment or express its concerns.
    a. Please describe the "adequate notice" that you issued to the public prior to making any changes to the website, as required by the Paperwork Reduction Act. Please provide supporting documents, including documents memorializing the notice.
    b. Please provide a list of webpages (and a description of the information that was contained on each one) that were eliminated from the EPA website in 2017.

16. ***OP:*** On March 24, 2017, you issued an agency-wide memorandum[5] on implementation of Executive Order 13777[6], which announced members of EPA's Regulatory Reform Task Force, appointed Samantha Dravis to serve as EPA's Regulatory Reform Officer, directed certain program offices to recommend rules for repeal, replacement, or modification, and directed all program offices to seek public input on existing regulations and report findings to the Task Force by May 15, 2017. On April 13, 2017, EPA issued a Federal Register notice: Evaluation of Existing Regulations[7]. The comment period closed on May 15, 2017 and EPA received over 460,000 comments, which were published online. The Task Force also led implementation of the Section 2 review in Executive Order 13783, Promoting Energy Independence and Economic Growth. EPA subsequently published a report pursuant to EO 13783 in October 2017. It is unclear whether the Task Force has been active since then or was involved in projects outside of what is discussed above. Accordingly, with regard to the Task Force, please provide us with:
    a. A complete list of who has or is currently serving on the Task Force, including their professional title and office at EPA, and their dates of membership on the Task Force.
    b. Please state whether the Task Force has consulted with non-EPA employees during the course of its work and, if so, please provide a list of their names and employers, and on what rules they have been consulted.

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[5] https://www.epa.gov/laws-regulations/memorandum-executive-order-13777-enforcing-regulatory-reform-agenda
[6] https://www.federalregister.gov/documents/2017/03/01/2017-04107/enforcing-the-regulatory-reform-agenda
[7] https://www.federalregister.gov/documents/2017/04/13/2017-07500/evaluation-of-existing-regulations

c. A list of meeting dates and topics for Task Force meetings held thus far and scheduled to be held this year. Please provide copies of any agendas that were circulated prior to each meeting.
d. All documents created by or for the Task Force, (including emails, memos, white papers, meeting minutes, correspondence, and comments that cannot be found on the regulations.gov website).

17. ***OEI:*** The Freedom of Information Act (FOIA) requires agencies to respond to a FOIA request within 20 days of receipt of the request. Although agencies are given some latitude to extend the response timeline in light of "unusual circumstances," EPA's failure to meet the deadlines specified in the Act has resulted in many FOIA requests left unanswered. That, in turn, has led to lawsuits against EPA for failure to meet the FOIA timeline.
    a. EPA currently submits open FOIA request logs to the Committee on a monthly basis, pursuant to an oversight letter sent to EPA on March 17, 2017. Beginning on the date of your next log submission, please also provide the number of currently open FOIA requests, the number of lawsuits that have been filed due to EPA's failure to comply with FOIA's deadlines, the number of FOIA lawsuits that have been completed, the number of lawsuits resulting in EPA providing the requested documents, and the cost of each lawsuit to the taxpayer.
    b. Does EPA follow the "rule of three,[8]" which calls on agencies to post frequently requested records to its public website? If so, please identify where those records are posted. If not, please explain why not.
    c. Please provide any internal EPA guidance that exists on the use of FOIA redactions. Please provide documents confirming that staff responsible for redacting documents have received the appropriate training.

18. ***OPA:*** During the hearing Senator Duckworth asked for "a detailed schedule of your meetings and receipts for international travel you have taken since being confirmed." You agreed to provide those documents. Since then, a report[9] detailed tax-payer funded travel you took internationally and domestically that included first-class tickets on commercial flights as well as travel on military jets. For each flight, international or domestic, that you have taken since you were confirmed, please provide the following information:
    a. Date of the flight, the departure city and airport, and destination city.
    b. Class (e.g. coach, business class, first class, or some other class of travel) and cost of the ticket.
    c. Source of funding for the ticket (e.g. federal taxpayers, the State of North Dakota, Heritage Foundation).
    d. For each non-commercial flight, please explain why a non-commercial flight was selected.
    e. Names of staffers who accompanied you on each trip, the cost of their flights, classes of their tickets, and the sources of funding for their tickets.

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[8] https://www.justice.gov/oip/oip-guidance/proactive_disclosure_of_non-exempt_information
[9] https://www.washingtonpost.com/national/health-science/first-class-travel-distinguishes-scott-pruitts-epa-tenure/2018/02/11/5bb89afc-0b7d-11e8-8b0d-891602206fb7_story.html?utm_term=.4c0713143235

f. Copies of all receipts of air travel for you and your accompanying staff.
g. For any ticket issued to you or your accompanying staff that was not a coach-class ticket (or its equivalent), please explain why it was necessary to purchase that class of ticket.

19. ***OAR:*** During the House Energy & Commerce subcommittee hearing on December 7, 2017, you testified that particulate matter is a "very important criteria pollutant" that should be regulated under the National Ambient Air Quality Standards (NAAQS) program. One study[10] found that PM2.5 "was the fifth-ranking mortality risk factor in 2015," and contributes to nearly 90,000 deaths in the US every year.[11]

    a. Do you agree with the general conclusion from this analysis that PM2.5 presents a serious public health concern? If not, please provide supporting evidence, including any research or analysis EPA has conducted, that supports your position.
    b. Please provide documentation supporting any analysis you have done to calculate the amount of PM2.5 pollution that will be created as a result of your actions to reverse, delay, or modify the Clean Power Plan, methane, and the Glider Kit rules. Please state whether you attempted to calculate the adverse human health effects that will be caused by your changes to the rules mentioned above.
    c. Do you think there is a tolerable level of PM2.5 that is appropriate for human exposure? If so, please specify it, and explain what evidence you have to support this.
    d. Are you aware that a study conducted by Tom Brewer at Tennessee Tech University determining that trucks outfitted with glider kits are as clean as new diesel truck engines is now under investigation for "misconduct in research" by Tennessee Tech University?[12] This is the same study that was included in the glider industry's petition asking the EPA to repeal emission requirement for glider kits and cited in the EPA's November 16, 2017 proposal to repeal the Emission Requirements for Glider Vehicles, Glider Engines, and Glider Kits. Please describe how you plan to re-assess EPA's November 16, 2017 proposal in light of the potential misconduct associated with this study. If no such plans exist, why not?

20. ***OAR:*** In response to questions from Chairman Barrasso regarding the implementation of the 2015 National Ambient Air Quality Standard (NAAQS) for ground-level ozone, you commented that the EPA was "in the process of designating attainment and non-attainment [areas] with respect to ozone." You went on to state, "when you think about ozone, there has been a lot of focus on whether the parts per billion, 75 parts per billion, reducing it to 70 parts per billion, was a wise decision. That has not been our focus. Our focus has been on more the issues and implementation that you have raised."

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[10] https://www.ncbi.nlm.nih.gov/pubmed/28408086
[11] "Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015." See Table 2.
[12] http://herald-citizen.com/stories/ttu-investigating-fitzgerald-study,25943

a. Do you agree with EPA's conclusion in 2015 that the primary NAAQS standard for ground-level ozone should be set at a level of 0.070 parts per million (ppm) to protect health with an adequate margin of safety? If not, why not?
b. Do you agree with the underlying science data for the 2015 NAAQS for ground-level ozone that finds ambient ground-level ozone pollution above 0.070 ppm can trigger asthma attacks in children that have asthma? If not, why not?
c. Do you agree with EPA's assessment that once implemented, the public health benefits from the 2015 NAAQS for ground-level ozone will outweigh the costs? If not, why not?
d. Will you confirm that under your leadership, the EPA will not weaken the 2015 primary NAAQS standard for ground-level ozone set at 0.070 parts ppm?

21. ***OAR:*** Under Clean Air Act section 111, can EPA base emissions guidelines on a "best system of emission reduction," if application of the measures comprising that best system of emission reduction would result in a source increasing total emissions of the regulated pollutant? Why or why not?

22. ***OAR:*** In determining the "best system of emission reduction" under Clean Air Act section 111, do you believe that EPA must consider the degree of air pollution reductions achieved? Why or why not?

23. ***OAR:*** The 2009 Cause or Contribute Finding concluded that the combined emissions from new motor vehicles and new motor vehicle engines of six key well-mixed greenhouse gases—carbon dioxide, methane, nitrous oxide, hydrofluorocarbons, perfluorocarbons, and sulfur hexafluoride (collectively, "GHGs")—contribute to greenhouse gas pollution that threatens public health and welfare. At the time, EPA cited data showing that in 2007, source categories regulated under CAA section 202(a) accounted for 23.3% of domestic GHG emissions, and the electricity sector accounted for 34.2% of domestic GHG emissions.[13] Do GHG emissions from the electricity sector cause or contribute significantly to greenhouse gas emissions that can reasonably be anticipated to endanger public health or welfare? If not, why not?

24. ***OAR:*** Do any parts of the Clean Air Act authorize EPA to decline to set 111 standards (or emission guidelines) for GHGs from stationary sources if there is an Endangerment Finding for GHGs entirely? If so, please specify them.

25. ***OAR:*** According to the most recent National Climate Assessment (NCA) released by the Trump Administration, climate change caused by emissions of heat-trapping gases "outweigh[s] other factors in determining burned area in the western U.S. from 1916 to 2003, a finding confirmed by 3000-year long reconstructions of southwestern fire history."[14] According to the NCA, "Numerous fire models project more wildfires as climate change continues," including "up to a 74% increase in burden area in California, with northern California potentially experiencing a doubling under a high emissions

[13] *See* 74 Fed. Reg. 66496, 66540 tbl.2 (Dec. 15, 2009).
[14] NCA at p. 468, *available at* http://s3.amazonaws.com/nca2014/high/NCA3_Climate_Change_Impacts_in_the_United%20States_HighRes.pdf.

scenario toward the end of the century."[15] The NCA calls conifer forests in southern California "notably threatened" by the climate change caused by heat-trapping gases. According to the Trump Administration's NCA, California is also at extraordinary risk from seal-level rise and coastal damage. Without adaptive action, the Trump Administration expects that critical California infrastructure such as the San Francisco and Oakland airports "are at increased risk of flooding with a 16-inch rise in sea level in the next 50 years . . . ." Increasingly high numbers of Californians will be put at risk of flood, including highly vulnerable populations less able to prepare, respond, or recover from natural disaster. On an even more fundamental level, emissions of these heat-trapping gases pose an exceptionally high risk to the highly urbanized population of California due to increasing urban heat. According to the Trump Administration, heat stress has been the leading weather-related cause of death in the United States since 1986 (when record-keeping began).[16] Severe heat waves such as the 10-day California heat wave of 2006 trigger "escalating effects" that kill people, particularly the elderly and those in low-income communities. Heat waves can also cause respiratory stress by expediting chemical reactions that cause the formation of ground-level ozone.

a. Do you agree that emissions of heat-trapping greenhouse gases cause compelling and extraordinary harm to the people and environment of California? If not, please explain why not, including whether you either i) do not accept the findings of the Trump Administration's NCA or ii) do not believe the impacts to California described in the NCA are compelling or extraordinary.
b. Do you agree that emissions of greenhouse gases from motor vehicles cause compelling and extraordinary harm to the people and environment of California? If not, please explain why not.

26. ***OAR:*** Please list each of the meetings that Administrator Pruitt, Assistant Administrator Wehrum, David Harlow or other EPA political staff (including EPA transition team officials) have held with outside entities, since January 20, 2017, on the topic of changes or "reforms" to the New Source Review or Prevention of Significant Deterioration requirements under the Clean Air Act. Please provide all documents received from outside entities, as well as any email correspondence between EPA employees and outside entities, on this topic, since January 20, 2017.

27. ***OAR:*** Please explain in detail how the policy options in the December 18, 2017 Advance Notice of Proposed Rulemaking regarding future rulemaking to reduce existing power plant greenhouse gas emissions would achieve the full range of public health, economic, and environmental benefits that would have resulted from Clean Power Plan.

28. ***OAR:*** In President Trump's June 1, 2017 statement announcing the United States would be withdrawing from the Paris Climate Accord, President Trump highlighted two studies - economic analysis from the National Economic Research Associates and a climate science study from MIT. These same studies were included in White House materials.

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[15] NCA at p. 468, *available at* http://s3.amazonaws.com/nca2014/high/NCA3_Climate_Change_Impacts_in_the_United%20States_HighRes.pdf.
[16] NCA at 471.

a. Did you, or any other EPA political staff, provide White House staff or the President information on these two studies?
b. Please provide a copy of all documents, (including but not limited to hand-written notes, paper files, emails, memos, white papers, telephone logs, presentations or meeting minutes) between and among any combination of you, other agency officials, other federal government officials, any state officials, and any non-governmental entities that inform, contribute to, direct, or are otherwise related to related to the Paris Climate Accord.

29. ***OAR:*** How many facilities subjected to MACT standards are also subjected to Reasonably Available Control Technology (RACT) standards that are more stringent or the same requirements for volatile organic compounds? Are there some parts of the country that are not subject to RACT controls for volatile organic compounds? If so, please list those areas.

30. ***OAR:*** Studies have found that regulations may play some small part in reductions in the coal workforce; but automation, shifts in mining practices, and prices of natural gas are all major contributing factors to the decline of coal.
    a. How many coal mines have closed or gone bankrupt since you became EPA Administrator?
    b. Please provide a list of every coal mine and coal-fired plant that will remain open, be built, or be expanded as a result of the rescission of the Clean Power Plan, along with the expected number of jobs that will be retained or added as a result. On what basis was each EPA projection made?

31. ***OAR:*** I remain concerned about the volatility in the Renewable Fuel Standard (RFS) compliance trading system used by EPA, known as the Renewable Identification Number (RIN) market and the impacts that RIN market manipulation is having on the economic stability of East Coast refineries.
    a. Currently, the EPA has a Memorandum of Understanding with the Commodity Futures Trading Commission (CFTC) on RIN market manipulation. In the past year, how often has EPA staff communicated with the CFTC on RIN market manipulation and what have you and your staff done with the CFTC to assess potential RIN market manipulation?
    b. In my conversations with CFTC officials, they indicate that you have not asked them to do much in assessing RIN market manipulation and suggested EPA is not collecting the right type of information to be able to assess potential manipulation. Why haven't you asked the CFTC to do more to help EPA prevent potential RIN market manipulation?
    c. I have asked the Federal Trade Commission (FTC) staff to offer their expertise to your staff. Has anyone at the EPA talked to FTC staff about ways the FTC can be helpful? Have you considered establishing a Memorandum of Understanding with the FTC to assist with RIN market manipulation?
    d. Will you commit to working with my staff to do more to address market manipulation in the RIN market?
    e. Will you commit to implementing the RFS fairly in a way that ensures an even playing field among obligated parties?

32. ***OAR:*** Under the Renewable Fuel Standard (RFS), biogas-generated electricity used to charge electric vehicles (EVs) is already an approved pathway and is eligible for the generation of cellulosic Renewable Identification Numbers (RINs). Applications for this pathway were submitted over a year and a half ago. Will you commit to approving an application for this pathway in the next 60 days?

33. ***OW:*** Aside from the type of water identified in *SWANCC v. Army Corps of Engineers*, which have no significant connection at all to navigable-in-fact waters, are there any categories of water bodies that you believe have such an insignificant relationship to navigable-in-fact waters that discharges into them should be exempt from the Clean Water Act? In those cases, would the federal Clean Water Act allow discharges of unlimited quantities of toxic poisons into those waterbodies, even if a portion of those poisons eventually flowed downstream to navigable-in-fact waters?

34. ***OW:*** The Obama Administration implemented its definition of "Waters of the United States" for several weeks in 2015. Has the EPA conducted any analysis of how easy or difficult it was to administer the Rule during that time? If not, why have you not conducted that analysis?

35. ***OW:*** In an interview with the National Cattlemen's Beef Association, you said that, "The Obama Administration reimagined their authority under the Clean Water Act and defined a 'water of the United States' as being a puddle …"[17] The Obama Administration rule expressly exempts "puddles" from the definition of "waters of the United States?" *See* 33 C.F.R. §328.3(b)(4)(vii).
    a. If you were previously aware of this exemption, why have you repeatedly mischaracterized the rule?
    b. If you were not previously aware of this exemption, do you retract your statement? If you will not retract your statement, please explain why.

36. ***OW:*** You also stated that the Obama Administration reimagined their authority under the Clean Water Act and defined a 'water of the United States' as being . . . ephemeral drainage ditches."[18] The Obama Administration rule expressly exempts "[d]itches with ephemeral flow that are not a relocated tributary or excavated in a tributary" "puddles" from the definition of "waters of the United States?" *See* 33 C.F.R. §328.3(b)(3)(i).
    a. If you were previously aware of this exemption, why have you repeatedly mischaracterized the rule?
    b. If you were not previously aware of this exemption, do you retract your statement? If you will not retract your statement, please explain why.

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[17] "EPA Administrator Scott Pruitt Urges Ranchers to File WOTUS Comments," https://www.youtube.com/watch?v=vTVd54WyhDQ.
[18] "EPA Administrator Scott Pruitt Urges Ranchers to File WOTUS Comments," https://www.youtube.com/watch?v=vTVd54WyhDQ.

37. ***OW:*** What specific provision of the Clean Water Act or Administrative Procedure Act gives EPA the authority to alter compliance dates, not merely effective dates, for standards lawfully promulgated under 33 USC 1311(b)(2)?

38. ***OW:*** The Clean Water Act prohibits compliance dates that extend more than three years from the issuance of new effluent guidelines (EGs). In what specific statutory provision did Congress allow EPA to flout that requirement by postponing until 2020 the compliance deadline of an EG issued in 2015?

39. ***OW:*** EPA explained that it is delaying the compliance deadlines of the steam electric power generating EGs because of costs to regulated industry. However, EPA estimated only 28% of coal-burning plants—and only approximately 12% of power plants overall—would incur any costs from the rule at all. Even among that small subset, almost all of those plants would incur costs less than 1% of the company's revenue.
    a. Do you disagree with those figures? If so, explain your disagreement.
    b. To what extent did you consider the EG's extensive public health benefits when deciding to delay the compliance deadlines?
    c. Do you believe that the incremental costs to industry outweighed the public health and environmental benefits of the EGs? If so, explain why.

40. ***OW/OGC:*** The Safe Drinking Water Act permits EPA to "fill not more than thirty scientific, engineering, professional, legal, and administrative positions within the Environmental Protection Agency without regard to the civil service laws." 42 U.S. Code § 300j–10. These appointments may be made where the Administrator deems such action necessary to the discharge of his functions as they relate to Title XII of the Public Health Service Act (42 U.S.C. 300f et seq.) (relating to safety of public water systems). These individuals are exempted from certain other Executive Branch requirements, including the Trump Ethics Pledge. In an August 18, 2017 letter to GAO, Senator Whitehouse and I wrote: "EPA has utilized its SDWA authority to hire a number of non-Senate-confirmed political appointees, some of whom are serving in supervisory positions and in roles that raise ethical questions." Based on documents provided by EPA, it appears that some individuals may still be serving as administratively determined appointees. These appointees have been permitted to work on projects with essentially no check on their ethical or financial conflicts. Also, many of these appointees appear to have had EPA e-mail accounts that were created and used by them for weeks and even months before their stated appointment date -- in some cases nearly 4 months before.
    a. What is EPA's policy on the length of time an employee is allowed to serve under the SDWA authority without having to complete a financial disclosure form, or complete a recusal statement (if necessary)?
    b. What safeguards are in place to ensure that employees hired under the SDWA authority do not work on matters that may trigger a conflict before they submit their financial disclosure form and complete any necessary recusal statement?
    c. For each appointee hired under the SDWA authority, please provide the date of their appointment; the date the appointment ended (if any); and the specific projects they worked on while serving as an administratively determined appointee.

d. For each employee hired by the EPA under the SDWA authority, Schedule C authority, or as Non-Career SES, provide the date on which their EPA e-mail address was created, and the date of their appointment, whether they worked at EPA in any capacity prior to their appointment date and if so, what capacity.

41. ***OPA:*** In response to questions from Senator Merkley, you testified that a "Red Team / Blue Team" exercise to re-examine the underpinnings of climate science is still "under consideration" at EPA. According to Jim Lakely, the communications director of the Heartland Institute, EPA has "reached out to the Heartland Institute to help identify scientists who could constitute a red team," and the Heartland Institute had been "happy to oblige."[19]
    a. Is Mr. Lakely telling the truth that EPA representatives reached out to the Heartland Institute for help identifying scientists who could participate in a Red Team/Blue Team exercise? If yes, why did EPA choose to contact the Heartland Institute?
    b. Have representatives of the Heartland Institute provided representatives of EPA with a list of "scientists who could constitute a red team"? If yes, who are the Heartland Institute's proposed participants?
    c. Have any EPA representatives consulted with any other organizations, corporations, or individuals about potential individuals who could participate in a Red Team/Blue Team exercise? If yes, provide the names of those organizations, corporations, or individuals consulted, and the names of any proposed participants.
    d. Do you know the names of any individuals or organizations who have contributed to the Heartland Institute? If yes, please provide the names of any such individuals or organizations with whom you have met in your capacity as EPA Administrator.
    e. Please provide a copy of all documents (including emails, white papers, meeting agendas, powerpoint presentations, memoranda and other materials) received or obtained by EPA related to the "Red Team/Blue Team" climate science effort.

42. ***OCFO:*** A press report indicates that EPA's Office of the Chief Financial Officer established a target for Region 9 to reduce their FTEs by 10% by the end of FY18. Has the CFO or anyone in the Administrator's office provided other EPA regional offices or program offices with targets for reducing personnel by a specified percentage? If so, please provide each of the targets. Please also provide any document from the CFO or the Administrator's office communicating an FTE or staff reduction target to any EPA region or program office for FY18 or future fiscal years.

43. ***OLEM:*** A recent report[20] indicates that, at a proposed superfund site in Chattanooga, EPA is only taking the most protective clean-up measures at properties where children currently live. EPA cannot possibly know whether families with children will one day

[19] http://www.washingtonexaminer.com/trump-administration-lining-up-climate-change-red-team/article/2629124
[20] http://amp.timesfreepress.com/news/local/story/2018/jan/15/dozens-chattanooghomes-sitting-toxic-site/461286/?__twitter_impression=true

move into homes that EPA isn't cleaning up because children don't *currently* live there. And EPA cannot possibly know which homes children visit frequently.

a. Is the policy described in the report accurate? If not, please fully describe any inaccuracies.
b. If the policy described in the report is accurate, please provide all documents (including emails, memos, white papers, analysis, meeting minutes and correspondence) related to any policy decision that limits the most aggressive cleanup measures to sites that currently have children residing on the premises.

44. ***OP:*** The President issued an Executive Order saying that for every rule an agency writes, two rules have to be repealed such that the net costs to industry are zero. However, the White House issued guidance on implementing this executive order that says that rules that address critical health matters could be exempted from the two-for-one repeal requirement. Does EPA plan to exempt its rule revising the Lead and Copper Rule from the two-for-one Executive Order? If not, why not, since the Rule does relate to a critical health matter?

45. ***OAR:*** Coal ash is laden with toxic pollutants and heavy metals, and is second only to mine waste as the largest industrial waste stream in country. On April 17, 2015, the EPA published a final rule regulating the disposal of coal ash, also known as "coal combustion residuals" (CCR), from power plants.[21] Among other things, the CCR rule established vital rules to protect groundwater resources, to protect local communities from toxic windblown dust,[22] to reduce the risk of catastrophic failure (*i.e.*, collapse) of surface impoundments, and to maintain records of compliance with those rules. You became EPA Administrator on February 17, 2017. On April 17 and May 31, 2017, lawyers for power plants asked to you reconsider a laundry list of provisions in the CCR rule. On September 13, 2017, you replied that, "After reviewing your petitions, I have decided that it is appropriate and in the public interest to reconsider the provisions of the final rule addressed in your petitions, in light of the issues raised in your petitions, as well as the new authorities provided in the recently enacted Water Infrastructure Improvements for the Nation Act, Pub. L. No. 114-322, 130 Stat. 1628 (2016)."[23]

    You appear to have granted reconsideration of every provision requested by the electric power sector in their two petitions for reconsideration. Is that a correct reading of your letter? If not, which provisions are you reconsidering?

46. ***OAR:*** Please provide a copy of all documents (including emails, white papers, meeting agendas, powerpoint presentations, memoranda and other materials) received or obtained by EPA related to the April 17, 2017 petition for reconsideration from the Utility Solid Waste Group, and the May 31, 2017 petition for reconsideration from AES Puerto Rico.

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[21] 80 Fed. Reg. 21,302 (Apr. 17, 2015).

[22] *See, e.g.*, Sabrina Shankman, *Is Coal Ash Killing This Oklahoma Town?*, INSIDE CLIMATE NEWS, June 13, 2016, *available at* https://insideclimatenews.org/news/10062016/coal-ash-killing-bokoshe-oklahoma-making-money-having-fun-cancer-asthma.

[23] https://insideepa.com/sites/insideepa.com/files/documents/sep2017/epa2017_1860.pdf

47. ***OAR:*** Section 2301 of the WIIN Act[24] allows EPA to approve state-administered CCR regulations to operate in lieu of certain federal CCR regulations. Will you ensure that any state programs you approve are at least as protective of human health and the environment as the EPA's 2015 CCR rule?

48. ***OECA:*** As a former state attorney general, you know that laws are only effective insofar as regulated entities believe they will actually be enforced. Could the unavailability of citizen enforcement make a state program less protective of human health and the environment, or is it irrelevant? Please fully explain your response.

49. ***OAR:*** For each inactive surface impoundment currently subject to the 2015 CCR rule, please provide:
    a. The site's name;
    b. The site's location;
    c. The amount of coal ash disposed of in the site;
    d. The number of people living within 3 miles; and
    e. Any waterbodies or public water supplies located within 3 miles of the site.

50. ***OAR:*** One of the companies that requested you reconsider the 2015 CCR rule, AES-Puerto Rico, appears to maintain a five-story pile of coal ash in Guayama, Puerto Rico. Has EPA received complaints about fugitive emissions from this waste pile? Has EPA investigated whether Hurricane Maria affected this and other waste piles in Puerto Rico? Please provide a copy of all documents (including emails, white papers, meeting agendas, powerpoint presentations, memoranda and other materials) received or obtained by EPA regarding off-site migration of coal-ash caused by Hurricane Maria. What precautions is EPA taking to ensure that weather events do not cause the release of coal ash?

Senator Booker:

51. ***OLEM:*** The EPA has conceded that dangerous toxic and carcinogenic substances at dozens of Superfund sites are not adequately under control. The agency has also acknowledged that recent hurricanes have washed unknown amounts of chemicals from multiple Superfund sites into waterways. A recent analysis showed that 327 Superfund sites, 35 of which are in New Jersey, are at a risk of flooding due to climate change. In response to these findings, the Government Accountability Office (GAO) has agreed to investigate the risks to human health and the environment posed by natural disasters' impacts on Superfund sites.
    a. Do you agree that EPA must design Superfund remedies that account for climate change?
    b. Have you directed EPA staff to determine which Superfund sites may require additional remedies or precautions to be taken due to climate change?
    c. Can you please specify any additional resources that EPA may need to help remediate these sites?

[24] Codified at RCRA section 4005(d), 42 U.S.C. 6945(d).

52. ***OLEM:*** On May 22, 2017, the Superfund Task Force was established to "provide recommendations…on how the Environmental Protection Agency (EPA) can streamline and improve the Superfund program." The report's recommendations were released in July 25, 2017. The EPA has stated that the Superfund Task Force kept no records of the analysis used to form recommendations for the Superfund program.
    a. Is this correct? Did the Agency keep no records of the analysis used to form recommendations?
    b. If it is correct, please provide justification or reasoning for the lack of record keeping when compiling a report that would shape the management of the Superfund program.

53. ***OLEM:*** In response to the Superfund Task Force recommendations issued on July 25, 2017, you developed multiple priority lists of Superfund sites, including a list for sites targeted for "immediate, intense action" and the "Redevelopment Focus" list that highlights sites that can create potential commercial and development opportunities.
    a. How did you pick the sites to include on these lists? What specific criteria did you use?
    b. What process do you intend to use in removing and adding sites to these lists?
    c. In what ways does the listing of these sites affect cleanup, construction, and revitalization efforts?
    d. Do you plan to release a report or follow up on the progress made at the sites on these lists?

54. ***OLEM:*** The Diamond Alkali site in Newark, New Jersey is on your list of Superfund sites targeted for "immediate, intense action" – will you be working as quickly as possible to implement the Record of Decision for the lower 8 miles of the Passaic River?

55. ***OLEM/OGC:*** When you commissioned the Superfund Task Force on May 22, 2017, you nominated Albert Kelly, who previously was CEO and President of Oklahoma-based SpiritBank, as its Chairman. Thirteen days prior to his appointment, he was ordered by the Federal Deposit Insurance Corporation ("FDIC") to pay a civil penalty of $125,000 after he "enter[ed] into an agreement pertaining to a loan ... without FDIC approval." Two months later, the FDIC issued a lifetime ban prohibiting Mr. Kelly from managing financial institutions after determining that his violations "demonstrated ... unfitness to serve as a director, officer, [and] person participating in the conduct of the affairs or as an institution affiliated party of the bank, [or] any other insured depository institution."
    a. The FDIC has banned Albert Kelly from banking for life because he "demonstrated ... unfitness to serve as a ... person participating in the conduct of the affairs ... [of] any ... insured depository institution."
        i. Will he be managing or providing advice on Superfund program funding or any other program funding in his role as Senior Advisor?
        ii. If so, what is the nature of these responsibilities?
        iii. Will you ask him to recuse himself from any specific agency activities or issue areas as a result of the banking ban?
    b. Were you aware of the FDIC investigations when you named him as Chair of the Superfund Task Force?

c. Were you aware of the FDIC investigations when you named him as Senior Adviser?

56. ***OLEM/OGC:*** Proper financial management of the Superfund program is critical to its success. Since 1999, federal funding for the Superfund program has declined from about $2 billion to about $1.1 billion annually, and the rate of contamination threat reduction at Superfund sites has declined. During your hearing, you repeatedly stated that you had visited states throughout the country and discussed the Superfund and that the cleanup of sites would require "direction and leadership." The Chairman of the Superfund Task Force is charged with developing and implementing recommendations to improve the work of the Superfund program.
    a. Mr. Kelly had no previous experience in environmental policy or management when you named him to Chair the Superfund Task Force.
        i. What experience did he have that you believe qualified him to serve as Chair?
        ii. What experience does he have that you believe qualify him to serve as your Senior Advisor?
    b. What responsibilities was Albert Kelly given as Chairman of the EPA Superfund Task Force during the production of the Superfund Task Force Recommendations? What is his role and responsibility as Chair now that the Task Force has released its recommendations?
    c. What responsibilities was Albert Kelly given as Senior Advisor at the EPA? What specific policy areas and programs will he be responsible for in this role?

57. ***OCSPP:*** When you decided to move forward with the process to potentially weaken the Agricultural Worker Protection Standard requirements, what steps did you take to comply with Executive Order 12898, which requires EPA to identify and address the disproportionately high and adverse human health effects of its activities on minority and low income communities?

58. ***OPA:*** Despite proposing drastic cuts to EPA's budget, you are spending taxpayer dollars on questionable expenses such as paying $25,000 to install a custom-made, soundproof phone booth in your office.
    a. Have you used this $25,000 phone booth for any calls with representatives of oil and gas companies?
    b. Will you provide to this committee within 10 days a log of all of the calls you have made from this phone booth?

59. ***OGC/OCFO:*** Despite a tradition of EPA reimbursing the Justice Department for their work in holding polluters accountable for Superfund clean ups, it was recently reported that you may break with this precedent, directing your agency to not reimburse the DOJ for that work. Do you plan on withdrawing EPA funding for the Justice Department's Environment and Natural Resources Division?

Senator Boozman:

60. ***OLEM:*** Administrator Pruitt, I understand that EPA is currently reviewing procurement guidance for the federal government's purchasing of lumber and wood products. During the Obama Administration, EPA issued procurement guidelines for lumber and wood products that called for the use of wood and lumber certified by the Forest Stewardship Council, leaving out wood grown on forests certified by the two major forest certification systems in the U.S.: the American Tree Farm System and the Sustainable Forestry Initiative. This guidance would have excluded of 4 million acres of Arkansas timber eligible for federal procurement. Additionally, the Obama Administration's guidance runs directly counter to the regulations issued under USDA's BioPreferred program, a program created in the 2008 Farm Bill that sets federal purchasing requirements for all biobased products and specifically recognizes eligibility from all three systems. What are you doing to ensure the EPA does not arbitrarily pick winners and losers and prevent the federal government from purchasing American timber?

Senator Ernst:

61. ***OAR:*** In two separate interviews shortly after the time of this hearing, you stated the need for both RFS reform and RIN reform. During the confirmation process, you went to great length to explain your intention to uphold the RFS. Can you please explain what you think RFS reform entails? In Iowa, this is a flashpoint and the continued rhetoric used appears to contradict your promise to this Committee on the RFS.

62. ***OAR:*** Much has been said about finding a "win-win" on the RFS and RINs, albeit not by you, but by some Members of Congress. Would you agree that fixing the Reid vapor pressure issue on E15 is a "win-win"? Doing so would reduce RIN prices, which some refineries say they need, while also expanding the marketplace for biofuels.

63. ***OAR:*** How aggressively will EPA pursue the RIN obligation from refineries that declare bankruptcy?

64. ***OCSPP:*** The Pesticide Registration Improvement Act (PRIA) was first enacted in 2003 and established a fee schedule for pesticide registrations. It lists specific time periods for EPA to make a regulatory decision on pesticide registration and tolerance actions submitted to the Agency. The goal of PRIA was to create a more predictable and effective evaluation system for affected pesticide decisions and couple the collection of individual fees with specific decision review periods. It also promoted shorter review periods for reduced-risk applications.

    PRIA has been tremendously successful, providing hundreds of millions of dollars in funding to EPA and providing product developers with clarity on timelines for Agency actions, and facilitating investment in research and development of new products. Importantly, through these industry fees, it has also provided $1 million annually in worker protection and pesticide safety training.

    PRIA has been reauthorized twice since it was first enacted – in 2007 and 2012 – each time by unanimous consent. It has been supported by large and small manufacturers of

agricultural and non-agricultural products, antimicrobial products, biotech companies, and biopesticides, as well as labor and environmental advocates. The current law was set to expire on September 30, 2017; however, an extension was included in the CR that extends the authorization through February 8, 2018. H.R. 1029, the Pesticide Registration Enhancement Act, which would reauthorize these authorities, passed the House by voice vote on March 20, 2017, and was reported by the Senate Agriculture Committee on June 29, 2017.

a. Can you explain the likely impacts to worker protection programs and your ability to regulate pesticides if PRIA is not reauthorized?
b. What would be the impact to farmers across my state and the country?

Senator Fischer:

65. ***OAR:*** In two recent television interviews, you discussed the need for RFS and RIN reform. Given your commitments made to this committee during the confirmation process that you would uphold the RFS, can you please elaborate on what you think RFS reform means?

66. ***OAR:*** How do you plan to approach the bankruptcy court case involving Philadelphia Energy Solutions? Do you intend to ask the refinery to honor their legal obligation?

67. ***OAR:*** If PES is allowed to use bankruptcy to avoid their RFS obligation, do you expect other refineries to follow this path?

68. ***OAR:*** I understand that several commercial-ready companies seeking approval of new cellulosic biofuel (D3) registrations have been told by U.S. Environmental Protection Agency (EPA) staff that the processing of such applications is currently on hold until EPA staff completes an internal review.

Because of the investment and long-term planning required to undertake these projects, it is imperative that new production of qualified cellulosic biofuels is approved as efficiently as possible. This will allow these commercial-ready businesses to gain the value associated with the D3 RIN production during this time of tight margins in the agriculture economy and signal to the marketplace that these gallons are valued, as the Renewable Fuel Standard (RFS) intends.

If EPA is currently delaying registration of new D3 production, the falsely low D3 production volume would affect not only today's market, but also the market for the coming year and beyond, through EPA's annual volumetric rulemaking for the RFS. This practice would systematically underestimate D3 production, and thereby undermine Congress's intent under the RFS to grow the cellulosic biofuel market.

Does EPA currently have new cellulosic registrations on hold until EPA staff completes an internal review?